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A MYOPATHIC FAMILY; WITH HYPERTROPHIC, PSEUDO-HYPERTROPHIC, ATROPHIC AND TERMINAL (DISTAL IN UPPER EXTREMITIES) STAGES.[1]

BY STANLEY BARNES.

INTRODUCTION.

SOME ten years ago an unusual type of muscular weakness came under my notice, and it was only after a careful examination that the case was eventually classified as a myopathy. Further inquiry then elicited a family history of "locomotor ataxia," as it was called, going back for several generations. An attempt was therefore made to interview all available descendants of the earliest case (No. 1), who is said to have suffered from "locomotor ataxia," but who died about a century ago. (See Family tree opposite p. 46.)

Many of these persons examined have appeared to be quite normal. Others have shown varying degrees of myopathic weakness; whilst yet others are clearly latent cases of the same disease, in whom a single sign (such as absent knee-jerks or ankle-jerks) is the only evidence of any abnormality.

The total number of descendants of Case 1, who probably was born about 1749 and is known to have died in 1836, is about 500. It has not been possible to obtain such records as were adequate for our purpose in some 200 of these cases, and these have been omitted from the genealogical table. Of those included in the family tree (284 in all), I believe the record is so far correct, either as a result of direct observation or from the detailed description of relatives and others, that it may be accepted for the purpose of determining the form

[1] Presidential Address delivered to the Neurological Section of the Royal Society of Medicine, January 21, 1932.

of inheritance. Altogether over 160 individuals have been personally examined either by my house physicians or myself, and this list includes nearly all the living myopathic members of the group, and all of those who were living in the Midland Counties during the last ten years.

The Family.

Apart from its affection by myopathy, the family appears to have been free from any unusual tendency to disease in the last 130 years. The various members throughout have remained at the level of the middle class, and have made their way with a sturdy independence without dropping in the social scale. The general level of intelligence is rather above than below the average for their social position, and great determination has been a marked characteristic of some of the later members. In a word, there is no such evidence of social decline or progressive degeneration as has been characteristic of the families of myotonia atrophica recorded by Fleischer, and by Adie and Greenfield: it corresponds more closely in this respect to those families in which dystrophy of the facio-scapulo humeral type has prevailed.

Cardiovascular disease is rare. Two of the cases (161, 171) examined have rheumatic mitral disease, neither of them suffering from muscular disease. One myopathic (No. 118) at the age of 40 was suffering from hyperpiesia at the time when he was first examined, the systolic blood-pressure being 170 and the arterial walls correspondingly thickened; his kidneys also showed signs of sclerosis in 1923, and he died in 1931 of secondary heart failure.

Cataract, skeletal deformities, absence of muscles or muscle groups (in particular of the sternal portion of the pectoralis major), are not present in any member of the family who has been examined, nor is there evidence of any such deformities to be suspected in others unaffected by myopathy when direct examination was impossible.

No member of the family, as far as I can ascertain, ever married another descendant of Thomas S.

The size of the families has been about normal, considering their social position. Celibacy, sterility and unusually large families have occurred with about the normal degree of frequency, if we take into account the social status and the times in which they lived. The record of abortions is nebulous so far as former generations are concerned; there has been no unusual number in the last fifty years.

At birth, the babies have not been remarkable for their size—they have been neither big nor little. The usual rule has been that in

infancy and childhood the growth of myopathic members was either normal or slightly subnormal, but at puberty a rapid increase in weight has taken place which brought them to over-average dimensions in this respect. As young adults they are strong and have tended to excel at games involving muscular power rather than agility; most of those examined after the age of 20 have been in good general health, of good colour and exceptionally well covered with subcutaneous fat of normal distribution. Throughout their adult lives, the myopathic members of the family have a robust appearance; after the menopause, which occurs at the usual age, the affected women tend to put on fat to an abnormal extent. In old age considerable loss of tissue—both muscular and fatty—is evident in the only case available (46), who has shown signs of progressive myopathy for over thirty years. But even at this age there is no suggestion of a "living skeleton" about him, and he is mentally as alert as ever.

In a majority of affected cases there is a tendency for the legs to be short in proportion to the length of the body. This feature must have been much more marked in Case 1 than in those living cases whom we have observed, for in the latter the disproportion is of such small degree that it would not be likely to have given rise to the nickname "Ducky" by which Case 1 was known.

In height, no appreciable variation exists between myopathics and non-myopathics, all being of medium height with normal degrees of variation. No evidence of endocrine disturbance has been found other than adiposity. In particular, none of the cases show signs of dystrophia adiposo-genitalis, acromegaly or dwarfism, and no case of hyper- or hypo-thyroidism has been seen.

Such cases of other forms of neuro-muscular disease as have been found are few in number; they will be discussed later.

On account of the late onset of the disease and its slow progress in a majority of those affected, they have not been so far crippled as to be unable to earn a full living during the reproductive period of life; as a result an unusually large number of the myopathics have married, and have transmitted the disease to descendants.

The Myopathy.

Perhaps the most interesting feature of this family group is the variation in the clinical picture at different stages. There can be no reasonable doubt that in all the cases the same fundamental inherited factor exists; yet a stranger to the family would probably classify one

case as a pseudo-hypertrophic paralysis, a second as the true Herculean type, a third as a distal type, and others as juvenile or transitional forms; one at least, on account of the myotonia of some of the muscles of the thigh, remotely resembles the myotonia congenita of Thomsen; whilst yet another was mistakenly diagnosed as a peroneal (neural) atrophy.

After examining many of the affected members of the family and learning their histories, I was forced to the conclusion that their varying forms represented, in the main, phases of the disease through which each member tends to pass. Nearly all of them are of heavy build, and the majority in their pre-myopathic state were of exceptional strength. In the only thin members affected (136, 209) there was no hypertrophic or pseudo-hypertrophic stage, progressive weakness with atrophy being the earliest features.

For convenience of description, four phases may be recognized—hypertrophic, pseudo-hypertrophic, atrophic and terminal. It need hardly be added that these stages merge into one another by a gradual process.

A.—The Hypertrophic Stage.

The first stage is that of true hypertrophy, and corresponds closely to that described by Spiller under the heading "dystrophia musculorum hypertrophica vera." I have selected two cases (Nos. 157 and 89), the first a girl, aged 9; the second, a man, aged 25; the former has been seen in this stage, and her description is direct. Case 89 was not seen by me until some ten years after the Herculean stage had reached its zenith, and is therefore an account based on the observation of others.

Case 157 is a girl, 9 years of age in 1923. Her outstanding physical feature is the magnificent development of the musculature throughout, but especially in the lower limbs. The joints are supple to the normal degree, but all movements are exceptionally powerful for the age of the child. This girl, though below the average age of her school class, was picked out as the central figure of a ballet on account of her finely-developed lower limbs and her exceptional capacity for toe-dancing. In height she is slightly above the average for age, but in weight and girth of limbs is much above the average of her compeers. Stance and gait, in walking or running, are perfectly normal. The muscles on palpation are firm like those of an athlete in training, but give no suggestion of toughness or fibrosis on handling. A discrimination at this early stage between the largeness of the muscles of the leg and those of the thigh leaves only a suggestion that the calf muscles are proportionately bigger than those of the quadriceps femoris group; for the latter are clearly above normal

size and power, though the presence of a good layer of subcutaneous fat makes accurate measurements impossible.

Both knee-jerks and Achilles-jerks are completely absent, even on Jendrassik reinforcement.

Her colour and general health are above average and the mental capacity well up to standard.

Case 89.—R. S., at 25, was a stockily-built man 5 ft. 9 in. in height and weighing 200 lb. He was unusually deep-chested, and his whole build suggested strength. Everywhere the muscles stood out in magnificent relief despite his goodly covering of subcutaneous fat. The calf muscles were large and firm, and the thigh muscles were on the same generous scale.

He stood erect, but not in any abnormal way. The muscles of the chest, shoulder-girdle and arms were finely moulded and of great size. They indicated correctly the great power of his arms in lifting and carrying. He was capable of lifting from the floor a 56 lb. weight between the thumb and finger of either hand. He could climb a flight of stairs with a load of 500 lb. on his back. About 1906 he attended a fair where a performing bear was wrestling with his keeper; in response to a challenge, he stepped forward, wrestled with the bear and laid it out! Realizing his great physical capacity, he became a furniture remover, and acquired both profit and pleasure in exhibiting his colossal lifting powers; but during the last twenty years the power of his legs has steadily diminished.

In the early years of his declining power the calves became larger than ever, and he often suffered pain in them on walking. So large did the left calf become that he was advised to consult a surgeon, and the latter came to the conclusion that a sub-aponeurotic lipoma was present. At the operation for its removal, nothing was found but a very large and fatty belly of the gastrocnemius muscle, of which unfortunately nothing was removed for section. Thereafter a rapid decline in power of his legs, progressive and still progressing, has occurred, and with it a steady diminution in calf measurement. Fig. 1 shows the appearance of this man in 1921, and figs. 2, 3 and 4 in 1931; they were taken in the third or atrophic stage.

B.—The Pseudo-Hypertrophic Stage.

The second stage marks the beginning of the decline in power.

Case 158.—A girl, aged 21 in 1923, is an example of this weakness. She is of unusual intellectual attainments, with very good general health and no suspicion of anæmia. Fully dressed she weighs 141 lb., and her height is 68 in. Her complaint is of an increasing difficulty in walking, noticed first after an attack of tonsillitis when she was 12 years old. The symptom to which attention was first drawn was a tendency to fall easily if her toe caught in any obstruction in bringing the foot forward in walking: to-day this is characteristically

FIG. 1.

FIG. 2.

FIG. 1.—R. S. (*Case* 115). 1923. Aged 37. Early atrophic stage. Note the well-developed torso, moderate thigh muscles and poor leg muscles. No lordosis. There were no reflexes in the legs at this stage.

FIG. 2.—R. S. (*Case* 115). 1931. Aged 45. There has been only slight advance in muscular weakness and atrophy of the legs. The muscles of the shoulder-girdle are large.

FIG. 3.

FIG. 4.

FIG. 3.—R. S. (*Case* 115). 1931. Aged 45. Lateral view. Increased adiposity.

FIG. 4.—T. S. (*Case* 89). 1931. Aged 57. A later stage of atrophy of the lower limbs. Much adiposity. Shoulder-girdle unaffected. No lordosis.

her worst symptom, as any slight irregularity of the ground which causes her toe to be held back a fraction of a second too long, results in a fall on to hands and knees.

The gait and stance in this patient would pass for normal except on close examination. Then it is found that in standing she is exceptionally upright, the knees being firmly locked in the fully but not abnormally extended position, the shoulders thrown well back and the chest and abdomen very slightly advanced. As she walks there is less than the normal forward inclination of the body at the hips, and each leg is swung forward loosely and with the foot a little higher than usual, until again the knee is locked in full extension; the heel is then brought sharply down to the ground and then the body weight is transferred to this limb by a jerky forward and lateral thrust of the other leg. The general effect is somewhat of a swagger of a loose-jointed kind; the family, who have lived with this gait in one or other of their relatives for years, call it the family "swank." As she walks on a stone pavement her relations can distinguish her gait at once by the sharp "clack" of each heel. She needs no artificial assistance and can walk a distance of two miles without undue fatigue, but beyond that limit is always conscious of an increasing ache in the calf muscles. She cannot run, and has not been able to do so since the age of 12 years. She can only pick up objects from the floor with great difficulty, unless she uses her free hand to help in sustaining the body weight whilst doing so. In getting up from the recumbent position, she "climbs up" herself in manner characteristic of cases of pseudo-hypertrophic paralysis. She is unable to stand without assistance if the knees are even slightly bent. All movements of the arms and trunk are of normal range and power, and there is no weakness in the muscles of the face or neck; speech, mastication, deglutition and closure of the eyes are all natural.

On physical examination the muscles as a whole are much above average size. In the upper extremity, power corresponds to size; in the lower, where the muscles are larger than would be expected in one of her build, they are much less powerful than would be expected. Owing to the goodly layer of subcutaneous fat, the muscles do not stand out prominently as in the usual cases of juvenile pseudo-hypertrophy, but their contour can be clearly defined during contraction on palpation. The calf muscles in particular are big, but their power is not much above half what would be expected of normal muscles of this size. The main weakness is in the extension of the knees, where power is barely a quarter of the normal; the flexors of the hips (ilio-psoas) have about half normal power. The tendon reflexes are absent throughout the lower limbs.

All the muscles of the upper extremities are fully normal, no wasting being present in the hands.

C.—The Atrophic Stage.

After passing through the pseudo-hypertrophic stage there is a gradual atrophy, with increasing weakness, in the muscles of the pelvic

girdle and in the lower extremities generally. At this period the cases show a sharp contrast between the flabby wasted muscles of the lower extremities and the powerful and well-developed muscles of the shoulder-girdles and arms. The only feature to which it is desirable to draw special attention is the fact that even late in this stage no muscle appears to be totally paralysed, though in some power is reduced to a mere fraction of the normal.

In one case (136) now living, the patient began her weakness with an atrophic process, there being no hypertrophic or pseudo-hypertrophic stage. It is noteworthy that this is the only case of fully developed dystrophy in this family in whom the bodily habit is (and always has been) thin. The distinctive features of this period, and in which the signs differ from those of the Charcot-Marie-Tooth type of peroneal atrophy, are :—

(1) A tendency for the proximal muscles to be more affected than the peripheral, the psoas-iliacus being particularly weak.

(2) A less complete loss of power in any individual muscle.

(3) A more even degree of wasting of the whole lower extremity group, there being in particular no suggestion of a racquet-shaped bulge near the hip.

(4) No sensory disturbance whatever. The tendon reflexes are absent in this stage, not merely in the atrophic lower extremities, but throughout the arms, in which size and power are still normal.

D.—The Terminal Stage with Distal Atrophy (Hands).

Case 46 is now 81 years of age. In his youth and early manhood he was of Herculean (true hypertrophic) build with the degree of adiposity characteristic of the affected members of the family. At the age of 30 he could carry a piano on his back, and could work at his trade as a furniture remover for twenty hours at a stretch ; if a piece of string was tied round his upper arm he could snap it by contracting his biceps.

At the age of 50 he began to get painful cramps in his calves after exertion, and from this time forth became progressively weaker on his legs. By the age of 72 (when first examined) he had reached a stage at which walking was only just possible without a stick ; the chief weakness was in the flexors of the hips, but all the muscle groups in both legs were of a power not more than 40 per cent. of the normal although no obvious loss of muscle tissue could be detected. At this stage there was noted for the first time a wasting in the intrinsic muscles of both hands ; the first dorsal interosseous muscles were severely, and all the other small muscles slightly but definitely, wasted and weak.

At the age of 82, he has ceased to be able to walk without personal assistance, and there is widespread weakness, nowhere complete, in the muscles

FIG. 5.

FIG. 6.

FIG. 5.—T. S. (*Case* 89). 1931. Aged 57. Note the normal thenar muscles and pectorales.

FIG. 6.—T. S. (*Case* 89). 1931. Aged 57. The pectoralis major in contraction. Face normal.

of both lower extremities. The lower half of each leg is involved in a gross œdema; the thigh muscles are now obviously wasted, and this is the more apparent as much of his adiposity has been lost. In the upper extremities, the atrophy of his hand muscles has advanced; weakness, and a degree of atrophy not quite commensurate with the weakness, is present in all the fore-arm and arm muscles, but is most marked in the flexors of the wrist and the long flexors of the fingers. The scapular group are only slightly weak and are not perceptibly atrophic. No tendon reflex can be elicited.

FIG. 7.—J. S. (*Case* 47). Aged 68. Atrophy of the radial interossei, but no *main en griffe*. The atrophy is typical of the terminal stage. This patient has no atrophy of the legs, but the tendon reflexes (knee and ankle) are deficient.

HISTOLOGY.

In only one case has it been possible to obtain material for section (Case 118). This patient was recognized as a myopathic member of this family in 1923, and was then found to have hyperpiesia and a hypertrophied heart. The blood pressure slowly increased and heart failure set in in the autumn of 1930. He died in February, 1931, at the age of 48. Dr. G. R. Bashford made a naked-eye examination of the body and removed certain fragments of muscles, no other examination being permitted. His report is as follows:—

"The body is in a fair state of nutrition. There is obvious wasting of the calves, thighs, gluteal and pectoral muscles out of proportion to that of the others. The first dorsal interosseous muscle in each hand is completely atrophied and the thenar and hypothenar eminences are slightly wasted.

"*Measurements.*—Calves, right 9 in., left 9 in.; thighs (6 in. above the

knees), right 13½ in., left 13½ in.; pectoral muscles, about 50 per cent.; gluteal muscles, markedly wasted.

"Portions of the gastrocnemii, soleus and adductor muscles of right thigh were taken for microscopical examination."

The portions of muscle removed were sent to Professor Haswell Wilson, who kindly prepared sections and the photomicrographs here produced, together with the following report:—

REPORT ON PORTIONS OF MUSCLE EXCISED POST MORTEM.

Sections, longitudinal and transverse, have been prepared from portions of the adductor magnus, gastrocnemius and soleus. Atrophic changes are present in each of these, but there is a marked difference in their intensity, being relatively slight in the adductor magnus and extreme in the soleus.

Adductor magnus.—In longitudinal section the muscle-fibres as a whole are attenuated in appearance. The cross striation is well preserved and there is but little increase in the interstitial fibrous tissue. Here and there, however, degenerated fibres are present. In these the sarcoplasm is swollen and glassy or granular in appearance; the striation has disappeared and in some cases the fibre is folded on itself within the sarcolemma. These changes are accompanied by proliferation of the sarcolemmar nuclei.

Gastrocnemius.—The changes are similar in nature but much more advanced. Practically all the muscle-fibres show degeneration, and striation is only occasionally visible. In most cases the fibres are granular or homogeneous in appearance. There is much proliferation of the sarcolemmar nuclei, and in places rows or clusters of nuclei indicate the remains of completely degenerated muscle-fibres. In some cases the fibres appear to shrink within the sarcolemma till they are no longer recognizable amongst the proliferated nuclei. In others the fibres become swollen and disintegrate. There is much new formation of delicate fibrillar connective tissue which separates the individual muscle-fibres, and with this there is some deposit of fat, though this is not extreme. There are many dense granular deposits of hæmatoxylin in degenerated sarcoplasm—evidently small areas of calcification.

Soleus.—No intact muscle-fibres are found in any of the sections, and only an occasional swollen cylinder indicates the remains of muscle substance. Its position is indicated by strands of hyaline fibrous tissue lying in fat. In this there are small collections of sarcolemmar nuclei or granules of calcification, but beyond this there is nothing to show the course of the muscle-fibres.

In some of the sections small medullated nerve-fibres are present. Though not stained by special methods it is obvious that these are degenerated. Many of the axis-cylinders have disappeared and the fibres have retracted within the nerve-sheath. The nuclei of the neurilemma have proliferated and there is some fibrosis of the nerve-bundles. There is no noteworthy change in the vessels.

The changes as a whole are those of progressive atrophy of the muscle-fibres, unaccompanied by any evidence of reaction except on the part of the

PLATE I.

FIG. 8

FIG. 9.

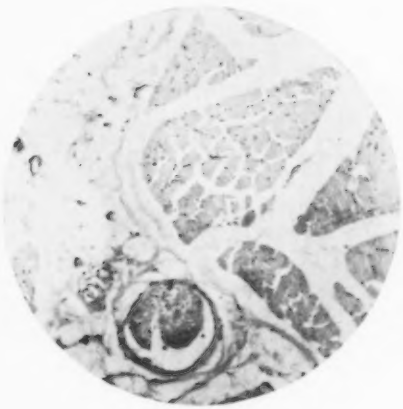

FIG. 10.

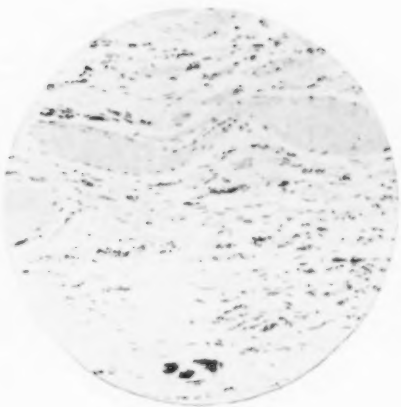

FIG 11.

FIG. 8.—Adductor magnus, longitudinal section. It shows the thinning of most of the muscle fibres and the proliferation of the sarcolemmar nuclei. × 100.

FIG. 9.—Adductor magnus, longitudinal section. A single normal fibre crosses the centre of the field : in it the cross-striation is visible. On either side of it there are degenerate fibres with numerous sarcolemmar nuclei. × 250.

FIG. 10.—Adductor magnus, cross section. The general shrinking of the muscle fibres is well shown. On one side of the section a small nerve is seen, which is retracted within its sheath ; fibrosis with increase in nuclei can be distinguished. × 100.

FIG. 11.—Gastrocnemius, longitudinal section. Swollen fibres cross the upper part of the field ; rows of sarcolemmar nuclei are seen along their edges. Below the muscle is almost replaced by fibrous tissue, in which are a few sarcolemmar nuclei. There is a cluster of three irregular areas of calcification. × 100.

To illustrate paper by Stanley Barnes.

PLATE II.

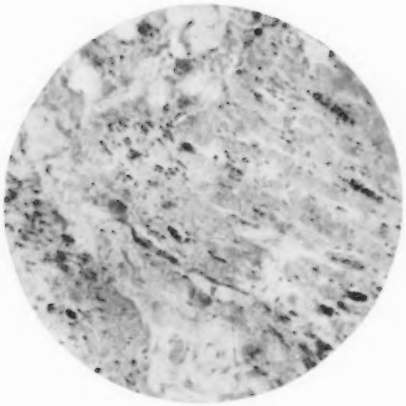

FIG. 12.

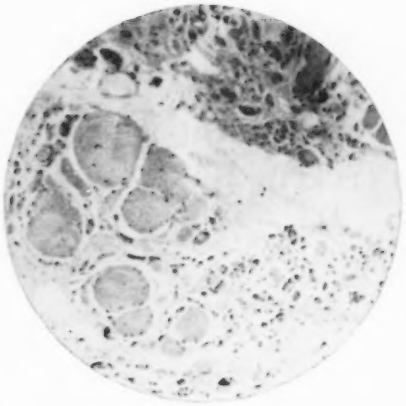

FIG. 13.

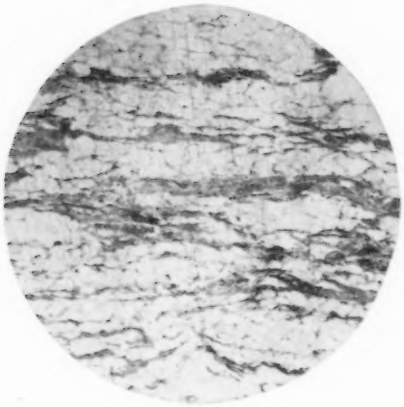

FIG. 14.

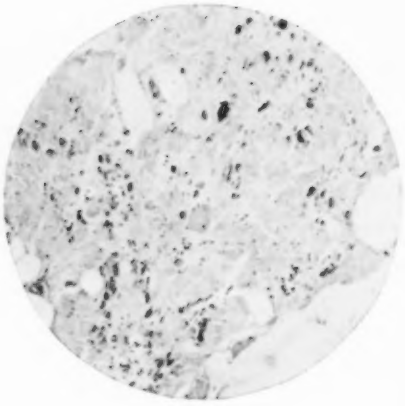

FIG 15.

FIG. 12.—Gastrocnemius, longitudinal section. The section shows a more severely damaged part of the muscle. Dark hyaline fibrous tissue occupies the greater part of the field, with some fat and a few rows of sarcolemmar nuclei. × 100.

FIG. 13.—Gastrocnemius, cross section. The section shows the contrast between swollen granular fibres and shrunken fibres marked out by sarcolemmar nuclei. × 100.

FIG. 14.—Soleus, longitudinal section. This shows extreme degeneration. The muscle fibres are represented by strands of dense fibrous tissue in which a few sarcolemmar nuclei are just visible. There is considerable deposit of fat between the degenerated fibres. × 50.

FIG. 15.—Soleus, cross section. A single swollen fibre is recognizable in the centre of the field. Elsewhere there is simply fibrous tissue with clusters of sarcolemmar nuclei and a small dark area of calcification. × 100.

To illustrate paper by Stanley Barnes.

sarcolemmar nuclei. There is no evidence of phagocytosis and no lymphocytic infiltration. The degenerated fibres appear simply to shrivel, or to swell up and gradually disintegrate. Fibrous tissue proliferation and fat formation are such as may be found in any organ undergoing atrophy, and neither is present to an excessive degree.

Diagnosis.

Although in the first instance there was some difficulty in determining the type of disease from which the patient was suffering, the examination of relatives who exhibited more advanced stages, together with the family history, soon left no doubt that the condition was a muscular dystrophy. The presence of pseudo-hypertrophy and absence of knee-jerks, the absence of all evidence of sensory defect or pyramidal disease, and the slow progress over long periods of time made no other diagnosis likely; the histological appearance of muscle sections confirmed the diagnosis. But the type of myopathy was unusual. The closest resemblance was to the pseudo-hypertrophic form; but from this it differed in that the inheritance was too direct, that the females were affected equally with males, and that the age onset was unusually (and nearly uniformly) much later than would be expected. Further, after the pseudo-hypertrophic stage the spread of the disease showed marked divergence from that type, for wherever the upper extremity was affected, the muscular weakness and atrophy were always of a distal type; it began in the intrinsic muscles of the hand, followed in the flexors of fingers and wrist, and only in the terminal stages affected the biceps, triceps and deltoid. Not only was lordosis never seen, but the sternal half of the pectoralis major, so frequently atrophied in the pseudo-hypertrophic form, has not been found deficient in any stage of any of these cases.

Similar contrasts separated out these cases from the Erb, Leyden-Moebius, Zimmerlin and Landouzy-Dejerine forms of the dystrophy. It is true that in the Herculean stage such cases as have exhibited this phenomenon conform very closely to the dystrophia hypertrophica vera of Spiller; whilst the type of upper extremity atrophy would compare with that seen in the distal forms described by Gowers, Batten, Spiller and others. But if we regard the clinical appearance as a whole, and not divorced from the course and progress of the disease, the cases in the S. family do not fully accord with any of the groups, and must be regarded as a variant, a special type of muscular dystrophy.

Clinical Features.

Age at onset.—One of the unusual features of this family has been that on the average the age onset of the dystrophy has been very late. Although some have begun at a late juvenile period, a large majority have not manifested any clinical symptoms of myopathy until reaching the ages of 35 to 50. For instance, it was only after her daughter (158) had been found to be myopathic that Case 91, at the age of 45, first showed evidence of the disease. Incidentally, the occasional late onset makes our table of cases a little uncertain; some are known to have died early, and are believed to have shown no sign of the disease, although a son (118) of Case 55 suffered from myopathy.

Individual cases of late onset of myopathies of most forms abound in the literature, but this point was particularly stressed by Cottin and Naville. In their series of cases, which were chiefly isolated and not directly inherited, and which particularly tended to be of a peripheral distribution, the age onset ranged as late as 68, and in females particularly several cases were described which began after the age of 40.

All observers are agreed that the Landouzy-Dejerine type has, as a rule, a later onset and is slower in its course than the pseudo-hypertrophic dystrophy; many cases of the former survive to late adult age, whereas in the cases of the pseudo-hypertrophic form the usual rule is that five-sixths of the cases are dead before reaching the age of 21 (Gowers).

To a small extent the family shows a tendency to "anticipation" of its myopathy in recent members. As to how far this is really true is difficult to say. The fact is that I have seen the more recent cases and have therefore been able to make a diagnosis at an early stage, whereas in the older ones I have had to trust entirely to the history given by patients or their relatives—who naturally tend to give a later age onset than I might have found. Nevertheless, in a few cases recently seen (such as Case 158) the onset was obvious to the family at puberty, whereas the tendency in former years had been for manifestations to appear for the first time at 35 to 50. In former generations the onset of the disease was nearly always too late to be a bar to marriage; in a few of the more recent cases it is clear that the chance of parenthood has been greatly diminished. Thus the family group of cases here recorded, although in clinical distributions and general characteristics resembling the pseudo-hypertrophic and juvenile forms of myopathy most closely, yet in its tendency to late age onset resembles the Landouzy-Dejerine and the distal types.

Not only is the age onset late, but the progress of the disease is unusually slow. In most cases of myopathic disease the tendency is for the progress to be intermittent, and this tendency is exaggerated in the S. family. The Herculean stage has lasted in at least two observed members for fifteen to twenty years; the pseudo-hypertrophic, where the affected muscles are larger but weak, continues for about ten years in some cases and much longer in others, before a gradual decline in size brings them to the atrophic stage. At least two cases still alive have been suffering from weakness of certain muscle groups for thirty years, and are still capable of getting about and of doing useful work.

In many of the cases, the onset of the disease or a rapid decline in power has followed a trauma or some intercurrent affection. Case 158 began after an attack of tonsillitis; Case 89 went downhill rapidly after the operation on his calf for the removal of a supposed lipoma; and these examples could be repeated indefinitely. Similar observations are recorded (often in non-familial cases) by many authors, as, for instance, by Hoffman (after severe scalds); Bramwell (after being buried by a shell-burst, and in a second case after a severe strain of the back); by Spiller (after a fall from a scaffold); by Robinson (several cases after strain, pregnancy and intercurrent disease such as enteric fever or influenza). In view of the natural tendency of all who suffer from a disease to attribute it to some outstanding event in their lives and to regard themselves as intrinsically normal, I think it is possible that in all such cases the effect of the disease or accident is merely determinant, and that there is not yet produced sufficient evidence to show that any normally constituted person can, as a result of such accident, develop myopathy.

In general it may be said that, given the necessary underlying constitution, the age onset is brought forward and the pace of the disease process accelerated by malnutrition, by conditions of severe strain, and by accidents or intercurrent disease.

Another unusual clinical feature has been the absence of lordosis. No single case has shown this symptom, and although the relative adiposity of the family may have masked the presence of spinal curvature to some extent, it is certain that no striking abnormality in this direction has occurred. In the same way, contracture has been notably absent at any joint, perhaps because wherever a muscle has been materially damaged its corresponding antagonists have never remained intact. Only in a very late stage of the disease, as in Case 136, is this rule broken.

Myotonia.

As an isolated phenomenon may be mentioned the tendency to myotonic contraction in the thigh muscles of Case 117. Ever since he was in the hypertrophic stage he has noted that any over-exertion affecting his thighs, and especially in cold weather, would cause a more or less painful cramp in the vastus externus and rectus femoris of the right lower limb. This cramp would last for several seconds, and always tended to be present more after the muscles had been resting than after a little preliminary activity. No similar myotonic contraction was seen in him elsewhere, and in no other member of the family was any similar condition observed.

The Absent Knee-jerk.

The early loss of the tendon reflexes has been a notable feature in the cases here recorded. In many members of the family no other suggestion of muscular or nervous abnormality has been found. In many cases no tendon reflex (biceps, triceps, &c.) could be obtained in the arms, although these limbs had normal power and their muscles were not wasted. A noteworthy case (157) is a girl aged 9, who resembled the dystrophia musculorum hypertrophica vera of Spiller, with abnormally well-developed legs and unusual power in all movements, and who on account of her strength and agility elected to become a professional dancer; and she had no knee-jerks.

In some of our cases pains in the limbs after exercise, cramps, &c., have been a prominent feature; but in none of them has there been any perceptible objective change in sensibility or muscle-sense, other than the loss of vibration-sense recorded in the advanced stage of the disease in Case 46.

A comparison with other forms of disease causing weakness of the quadriceps femoris, and due to damage to the central or peripheral nervous system, shows that a fairly severe loss of power and muscle substance may occur whilst the knee-jerk is only proportionately diminished. In his paper on Thomsen's disease (myotonia congenita), Rosett mentions that he found on occasion the same absence of the tendon reflexes without any corresponding atrophy, whilst the myotatic irritability remained normal; and, as many of his patients suffered from muscular pains, suggested that "some nerve elements are involved in the disease."

Towards the end of his clinical career, that acute observer, Sir William Gowers, used to say that congenital absence of the knee-jerk

occurred in about 1 in 10,000 cases; that is to say, after an exhaustive examination in which he had been able to elicit no knee-jerk, he could find no neuro-muscular pathological condition which would explain the phenomenon. I know of no published figures on this subject, nor can I produce any figures of my own. In common with other neurologists, I have met with the same phenomenon on several occasions, and the impression I have received is that the frequency-rate is somewhat higher in the Midland area than the London experience of Gowers would suggest. Oppenheim regarded the Westphal sign in these cases as one of the stigmata of degeneration, and remarks that it is so exceedingly rare that in practice it need not be taken into consideration.

In our group of cases, the examination of "healthy" members was made with the object of eliciting any facts which might give a clue to dormant disease. For this reason it was found possible in the cases whose knee-jerks were absent, whilst the muscular condition otherwise appeared to be normal, to indicate the probability that the absent knee-jerk here depended upon the muscular abnormality.

Only a prolonged examination of the family records of such cases will determine whether the suggestion is correct that the Westphal sign in apparently healthy individuals is to be regarded as a "stigma of degeneration" in a general sense, or whether, as I believe to be the case in the S. family, it is evidence of latent disease of a specific type.

Adiposity.

A characteristic feature of myopathic members of the family is a constant tendency to adiposity. With one certain and one possible exception, all the myopathic members have been heavily built in the early stages of the disease; not only are muscles and bones above average size, but the panniculus adiposus is always above average thickness. As the disease progresses beyond the pseudo-hypertrophic stage, the atrophy of muscle tends to be masked by a further increase in the fatty layer. In a few cases, the adiposity during the later stages of the disease has been of a gross type, weights of over 230 lb. having been recorded; but as a rule such cases as have lived beyond 70 years have shown a tendency during their senility to lose much of the added fat.

Apart from the adiposity and the tendency for all the myopathics to be of big general build, there has been a remarkable absence of any family tendency to skeletal or other defects. Thus abdominal herniæ, muscular asymmetry, absence of particular muscles, scoliosis, &c., have

not been noted; whilst signs of sexual or mental deterioration have been absent.

A large majority of the non-myopathic members of the S. family were definitely not adipose. Unfortunately, the case record does not in all cases state this fact, but a recent series of re-examinations of some thirty living relatives, and the observation of one of the most interested of the myopathic members (who has a comprehensive knowledge of the branch of the family derived from No. 5) confirms the opinion that all the "big" members become myopathic sooner or later. In no observed case has a non-myopathic member been found on examination to be adipose, though there is a record that Case 66 (who died 24 years ago) reached a weight of 280 lb. and lived to the age of 73 without becoming paralysed.

Of exceptions to this rule in adults there are one certain and one possible. Case 136 is a woman who is, and always has been, of slender build; weight about 110 lb. and height 61 in. Case 47 is a doubtful one; he has atrophy only of the interosseous hand muscles, and no other muscular weakness; he has always been lightly built, with a thin covering of fat. With these exceptions, all the myopathics are adipose, and all the non-myopathics appear to be normal in this respect. The adiposity tends in all cases to come on at about puberty, and is universal in its distribution. There is no case of dystrophia adiposo-genitalis in the whole of the examined cases; in fact all the evidence we can collect suggests that as regards fertility, the age of onset of puberty, and of the manifestations of secondary sexual characteristics, they are normal.

Signs of vegetative disturbance, such as cyanosis of the extremities, exophthalmos, myxœdema, &c., have been consistently absent, except (as in Case 46) where the paralysis has reached a high grade and the œdema and cyanosis of the feet may be regarded as a late effect secondary to the immobility, and to some extent dependent upon incipient heart failure.

Thus all the evidence we have collected from this family goes to show that the two conditions of myopathy and adiposity are present together, and that no other endocrine defects tend to occur with unusual frequency. Further, an adipose *forme fruste* comparable to the "Typ" of Diehl, Hansen and Ubisch, does not occur in the S. family.

As to whether the myopathy is secondary to the endocrine defect responsible for the adiposity, or as to whether both are dependent upon the same genetic factor, is a point which has been discussed by many authors (Diehl, &c., Robinson, Timme, &c.), who have already noted

this close association, and at this stage it would seem that no definite statement can be made. At the same time it should be noted that many myopathic patients do not exhibit adiposity; that some do not show any type of endocrine disturbance till long after the disease has developed; and that no satisfactory instance has yet been recorded in which dystrophia musculorum progressiva has arisen in the absence of a genetic defect of a myopathic character. On the whole, it is probable that the inherited defect responsible for the paralysis in our S. family is also causing the adiposity as a less important defect, for in some of the S. cases indications of myopathy (such as loss of knee-jerk) occurred first, and in most of these the adiposity manifested itself at a stage when the muscles were large and powerful. Such a conception of the mutant gene constituting the inherited morbid factor, is on all fours with observations recorded by the geneticists. As Morgan says (p. 304): "It must not be supposed . . . that mutant changes produce only single striking or even a single small change in one particular part of the body . . . Even in those cases where one part is especially modified, other effects are commonly present in several or in all parts of the body."

Abortive Forms, &c.

It has already been remarked that the family has been relatively free from other neuro-muscular diseases which must be regarded as endogenous. The myopathy has "bred true," and has not varied in its essential characteristics and course in any of the clearly defined cases. There are, however, a few cases of disease in the family which call for special notice. Case 177 (Emily S., aged 18) suffers from infantile hemiplegia and epilepsy; her father (Francis S.) has been examined and shows no sign of myopathy at the age of 56 and can now be presumed to be free from the inherited taint; there is thus a strong probability that the illness is in no way connected with the family disease. Case 188 was born deaf and dumb; his mother (of the S. family) at 47 is also free from any taint of myopathy. Case 123 was a boy born in 1882 who died when 5 years old, and of whom no record is available other than that of the parents; his father (Case 61) died in 1884 and was myopathic. This boy never walked; he was only able to shuffle along on his buttocks. He was an uncle of Case 177 and also to the family of Case 124, in which twelve out of thirteen children died before reaching the age of 10. There is thus a strong suggestion that some recessive factor has been introduced into this branch of the family, and

is partly or wholly responsible for the exhibition of disease. Case 168, belonging to a different branch of the family, is a Mongolian idiot. His mother is not myopathic, but two of her brothers and their father were so affected. It is again more likely to be due to some other recessive factor, inherited presumably from both father and mother, and independent of the myopathic taint, that the Mongolian condition arose.

Perhaps the most interesting member of this group is Case 47. Of the seven siblings derived from Case 12, five showed myopathy, one died childless at 50 and was free from disease, whilst their brother (Case 47) at the age of 68 has recently developed atrophy of the radial group of the intrinsic muscles of the hands. The atrophy is evenly bilateral, and does not correspond to that produced by pressure of cervical ribs; there are no signs that progressive muscular atrophy of a spinal type is developing; careful examination has excluded all the ordinary causes of such atrophy. I am inclined to the conclusion that in this case we are dealing with an undeveloped form of the disease in which hand atrophy is preceding pelvic girdle weakness, and in which the disease factor has lain dormant for an unusually long time. This view is supported to some extent by the fact that the ankle-jerks were absent even on reinforcement, although the legs showed no sign of weakness. The variation in the character of the disease in this case is all the more noteworthy in that (with one exception, Case 136) he is the only affected case seen in late middle life in whom the bodily habit has been slender. All of his children, none of them being yet 45 years of age, are so far free from myopathy.

It thus appears that, in this family, aberrant forms of the disease, if they exist at all, are exceedingly rare, and that if the disease exhibits itself in any way it is apt to progress in the same orderly fashion in all members of the family.

These results correspond fairly closely to other observations made on families when the disease has been transmitted in the dominant mode, but differs materially from what has been found in other groups. Notably is this so when isolated or small numbers of cases only have occurred in family groups. Davidenkow and Kryschowa (1930) found many conditions, especially in the mothers and relatives of myopathics, in whom no true dystrophy was present but in whom neuro-muscular anomalies existed which in their opinion were indications of an underlying defect; included in this list were ptosis, big calves, deformities of the sternum, imperfections of the abdominal muscles leading to hernia, and anomalies of the vegetative system. In the cases of Diehl, &c., no

such variety of defects occurred; but a single well-defined type (adipose, stunted growth, sloping shoulders, &c.) was frequently seen and appeared with such regularity that they formulated the theory that in their myopathic cases the mode of inheritance was a double (dimeric) dominant, and that the adipose types were those members of the family who carried one only of the factors necessary to the manifestation of myopathy. In relatives of Minkowski and Sidler's cases, arising as an explosive outbreak similar to that which has been noted in myotonia atrophica by Fleischer, there were found no cases of idiocy, stunted growth, &c. The most notable general feature of their family group was the very high infantile mortality in the generation to which the patients belonged as compared with that of their parents.

Many records of individual cases are available in the literature where arrested forms of myopathy are believed to have been met with (Bramwell, Marina, &c.), that is, a non-progressive muscular weakness existed in cases where no other diagnosis could be accepted. It is probable that in some of these the disease was true myopathy of late onset and of very slow development, comparable, for instance, to what has been found in our S. family in Case 46 at the age of 50, or in Case 157 at the age of 10. Unfortunately in a large series of the older records no observations are reported of the physical condition of ancestors and their collaterals, which might have brought to light forms of aberrant defects suggesting a defective family trait, not frankly myopathic. It is of great importance that, in dominantly as well as recessively-transmitted cases, such records should be brought together in order that a judgment might be formed as to how far the various kinds of *formes frustes* are fortuitous, and how far they are to be regarded as phases of an underlying myopathic basis, not exhibiting true myopathy, either because of the absence of some other factor, or because other constituents of the genotype are able to hold in check the manifestation of muscular dystrophy.

For the moment the various *formes frustes* which have been described may be divided into two classes. The first will include all cases in which there are present features typical of myopathy, such as exceptionally big calves, absence of the sternal portion of the pectoralis major, partial defects of various muscles (especially the orbicularis palpebrarum) and perhaps congenital absence of tendon reflexes. These defects are specific, in the sense that they form features of various forms of myopathy, and may be either cases of arrest or of long-continued stabilization. The second group of *formes frustes*, less generally accepted and still requiring further investigation, consists of a series of physical defects

of a less specific type, in that they are not persistently present at any stage in myopathics; these defects include adiposity, stunted growth, gigantism, acromegaly, and other indications of endocrine damage or imbalance of congenital origin.

Polymorphism.

Such polymorphism as is seen is often more apparent than real. In the S. family there have been seen at varying phases forms which from the distribution of the damage and the size of the muscles might be classified as either hypertrophic, pseudo-hypertrophic, juvenile, and even distal; but a careful analysis of the histories shows that such polymorphism is here dependent upon the stage of the disease at which the observation is made, and that all of the cases tend to pass through these four phases. It is true that in several members, and particularly in Case 136, the only myopathic of the group who was thin, there is no record of a hypertrophic or pseudo-hypertrophic stage; the disease here began with atrophic weakness in the legs. Similar observations by other authors (Schultz, Keferstein, Weitz, &c.) suggest that we should regard pseudo-hypertrophy as a characteristic but non-essential element of the disease, which will occur in certain types of myopathy provided that its exhibition is not prevented by endogenous or exogenous factors which are independent of the specific factor causing myopathy.

In a few cases in the literature there have occurred diverse types of myopathy in particular families. Weitz, in his careful review, collected a series of such cases together, and compared them with his own and other groups. Briefly the conclusion at which he arrived, and which the record of the S. family supports, is that there is a constant tendency for the cases in each family group, and especially for those directly inherited, to appear in the same form and at the same age. The rule is often broken in the case of age onset, and this is to be attributed partly to endogenous factors involving genes other than the mutant responsible for the myopathy, and partly to exogenous conditions such as defective nutrition, strains and intercurrent disease. The development or absence of pseudo-hypertrophy would appear similarly to vary greatly in such groups, and is also probably conditioned largely in the same way by both endogenous and exogenous factors. In a few cases, as for instance those of Schumacher where one case of twins was of the Landouzy-Dejerine type and the other pseudo-hypertrophic, it is possible that the mixing of the types was due to two different strains of myopathy being inherited, a condition which must be as rare as is the

solitary observation. From the point of view of its genetics, the facio-scapulo-humeral form stands out almost, but not quite, as a separate entity; whilst the other forms—pseudo-hypertrophic, juvenile, hypertrophic, &c.—though tending constantly to appear in the same form in other members of the same family, will show considerable variations in age onset, in distribution of the muscle atrophy, and in the presence or absence of pseudo-hypertrophy.

The distal form (Oppenheim, Gowers, Batten, Spiller) is so rare, and such a small number of family groups have been recorded, that little can be said of its genetics. It seems certain that it exists as an entity, and is distinct from the Charcot-Marie-Tooth form of peroneal atrophy. In our own group, Case 136 at one stage (in 1916) showed signs so closely resembling the neural type that a mistake in diagnosis assigned it to the latter group, the atrophy being present in distal form, slightly in the upper extremities and widespread (though mainly peripheral) in the lower. It was only when this case was known to be associated with the family, and it had been found that all the S. cases in a late stage developed atrophy in the intrinsic muscles of the hands, that the diagnosis could be corrected. Atrophy of this type commencing in the hand muscles is evidently very rare except in the true distal form, and occasionally as a *forme fruste*. I have been able to find no record of another case in which such a distal atrophy began in the upper limbs when the myopathy in the lower ones was mainly proximal. In this connection it is interesting to remember the family recorded by Thompson, who found that over five generations seven individuals out of sixty-four developed atrophy of the hands comparable with that in the S. family, but without any other sign of either myopathy or neural atrophy; the author was of opinion that in his cases the atrophy was secondary to cervical ribs, and that the latter had been the primary inherited factor.

Thus, so far as the dominant families of myopathy are concerned, it is rare to meet polymorphism if that term is used to indicate essentially different types of the disease; but it is common to find types which have a superficial difference from the expected form, but which in reality are only phases in the course of a long-drawn-out and kaleidoscopic clinical picture.

Inheritance.

The conclusions which Mendel reached as a result of his investigation into the results of breeding in plants have been subjected to all manner of tests in many different species, and are accepted to-day

fundamentally unaltered. "The theory postulates the existence of a number of individual particles of substance in the germ-plasm each of which controls the development of some particular tissue or character in the developing organism. It demands that in respect of any particular character the individual must receive from its parents, one from each, through the gametes, two factors, either similar or dissimilar,

Case No.		Affected		Not affected		Totals		
Sex (Parent)		M.	F.	M.	F.	M.	F.	M. and F.
M.	1	2	—	2	—	4	—	4
M.	5	2	3	—	1	2	4	6
F.	10	—	—	—	1	—	1	1
F.	11	1	—	2	2	3	2	5
M.	12	3	3	1	—	4	3	7
M.	15	5	3	—	1	5	4	9
M.	46	1	1	—	3	1	4	5
F.	49	—	—	—	2	—	2	2
F.	50	1	—	2	2	3	2	5
F.	51	—	—	1	3	1	3	4
M.	52	2	—	—	3	2	3	5
M.	60	—	—	2	—	2	—	2
M.	61	—	—	2	3	2	3	5
M.	63	—	—	1	2	1	2	3
F.	64	1	1	2	1	3	2	5
M.	65	—	1	4	—	4	1	5
F.	67	—	—	3	1	3	1	4
M.	89	1	1	—	—	1	1	2
F.	91	1	1	1	—	2	1	3
M.	115	—	1	2	3	2	4	6
M.	117	1	1	3	3	4	4	8
M.	131	1	1	7	3	8	4	12
14 M.) 8 F.)	22	22	17	35	34	57	51	108
		39		69		108		

according to whether or not in respect of this character the parents were alike or different. . . . It postulates that the association of dissimilar factors within the zygote is not attended by any adulteration effect upon them" (Crew).

In recent years the wide range of experiments carried out by modern geneticists has confirmed the theory and has enabled them to build up a new science. As to how far their results agree with the observed facts of human inheritance must be of absorbing interest to neurologists, and I propose to investigate the records of the S. family, and other published myopathic family groups, to determine whether in the first place the modes of inheritance can be so interpreted on Mendelian lines as to lead us to suppose that in all cases the inherited factor is a *sine qua non*; and, secondly, to determine if possible whether all the differing clinical types of myopathy are dependent upon an identical causal factor.

Mendel's second law—the law of segregation and of independent assortment—requires that if inheritance is in the dominant form, not only shall some of the first filial generation show evidences of the special character, but that the members of that family so affected shall be roughly one half. Seeing that the assortment of factors in the gametes takes place at random, it may easily happen that when members are small, as in the members of a human family, wide variation in the percentage may occur; but wherever a considerable number of cases can be brought together, the fifty-fifty ratio should be approached. Further, it will follow that in cases in which the inheritance is of a pure dominant type, no member of the later descendants of the family should show signs of the variant factor unless one of his parents also exhibited it.

Parents myopathic	Cases affected in Family Groups.		
Males	Sons	Daughters	
14	18	15	Affected
	24	22	Unaffected
Females			
8	4	2	Affected
	11	14	Unaffected
Percentages	Males	Sons affected	43 per cent.
		Daughters affected	41 ,,
	Females	Sons affected	27 ,,
		Daughters affected	14 ,,

Analysing our family group for this purpose, we find that in each generation (P_1 the parental, to F_5 the fifth filial) the disease has appeared. Further, of those myopathics who married and had families, but excluding as doubtful Case 47, and including as myopathics all who had absence of knee-jerks, we find that in 22 families in which either father or mother was myopathic (and where the other parent was presumably free from the taint), there were 108 children in all, the myopathics being 39 and normals 69, the percentage of the children showing myopathy was thus 38. In the 14 families where the affected parent was the father, 18 sons were affected out of 42, and 15 daughters out of 37; in the 8 families where the mother was the affected parent, 4 sons out of 15 and 2 daughters out of 14.

Setting out the totals in a different way, we may say that in cases where the affected parent was a male, 43 per cent. of sons and 41 per cent. of daughters were affected; where the mother was affected, only 27 per cent. of sons and 14 per cent. of daughters showed myopathy.

Admitting that the figures are too small for any final conclusion, yet they are large enough to be significant, and to indicate that some special factor is operating if Mendel's law is being followed. Probably the most important factor is an inherent defect in the genealogical table if it is taken at its face value. Just as the older section of the family tree may be imperfect in that it depends upon the memories and records of descendants, and that the cases dying before 1921 have not been personally examined, so the most recent section is vitiated by reason of the youth of many of the persons indicated. It has already been observed that many cases have shown no sign of the disease obvious to relatives until well on in middle life, and in some cases not till 60 years has been reached; and although a medical examination may have shown the first elements of the myopathy at an earlier stage, yet no case could be certified as free from the possibility of future disease until at least the age of 45 was reached. Case 46, though now suffering from an advanced stage of myopathy at the age of 81, only began to be obviously affected at 50. Significant also in Case 118, whose parents were both believed to be free from the disease, though he suffered from it; this unique departure from the family rule of inheritance can only be attributed to his mother having died at the early age of 30, and before she had reached the age at which the disease is usually manifested in this family. When this patient first came under my notice, it was the unusual character of his myopathy and its correspondence to that of the S. family which enabled me to direct his attention to the relation-

ship to the S. family; a fact of which he had not been aware previously.

Any attempt to eliminate from our case list all families in whom the children of myopathics have not yet reached the age of 60, involves us in making a record largely on unobserved cases, and is probably less trustworthy than the inferences to be drawn from the list as it stands. But if we allow for the presumption that some at least of the younger "unaffected" cases will develop the disease in later years, the figures will approach the fifty-fifty ratio.

To sum up: in the S. family the disease has been transmitted by males and females, who have been affected in about equal numbers; it has appeared in each generation, and has never appeared in any descendant of Case 1, whose parent did not exhibit the disease, with the one exception where the early death of a potentially affected parent prevented the exhibition of the myopathy. Finally, the ratio of affected to unaffected children is substantially what would be expected in inheritance of a dominant type.

Other Myopathic Families.

A considerable number of myopathic family groups are now to be found in the literature. Unfortunately, in most of them the numbers are small, and it has not been possible to trace back evidence of the disease through more than a very small number of generations, and in some no examination of relatives reputed to be normal has been possible on such a scale as is necessary for any final conclusion to be drawn as to whether the disease was inherited. In some groups, however, many details are available, and it is interesting to determine how far the forms of inheritance which are brought forward or can be deduced correspond to those in the S. family.

Robinson collected a number of cases all occurring in one family, and all being of one type. In the course of the five generations through which the disease was traced, the family had scattered somewhat widely through different States, but he was able to collect records of 128 children of affected parents. Of these there were affected 82 (or 64 per cent.), the proportion of boys affected being 65 per cent., and of girls 63 per cent. The myopathy affected the shoulder-girdle group of muscles almost exclusively, neither face nor lower extremities being damaged; the regular age of onset was puberty, and a little earlier in girls than in boys. In this group the inheritance was clearly of the dominant type.

Weitz, in 1921, recorded a series of cases of his own, and analysed in addition all those in the literature where sufficient facts had been given from which conclusions could be drawn. He found that of familial cases (35 families) there were 94 affected (72 males and 22 females), and 101 healthy (43 males and 58 females). He noted also that in the directly inherited cases the disease tends to assume a less severe form than in the sporadic or isolated ones. In the former type also, he notes that variations of a minor character only occur in a family, and that although the age-onset tends to be the same in each generation, this rule is often broken; anticipation at an earlier age in later generations was not the rule in most cases. He came to the final conclusion that the inheritance takes place either in the dominant, simple recessive or sex-linked recessive form, and that many cases must be explained on the supposition that new mutations have arisen.

Niwa, in a short record of three dystrophic families, found that the transmission was direct through males and females in the Landouzy-Dejerine type, and indirect (sex-linked recessive) in the pseudo-hypertrophic. He made the interesting observation that blood grouping is not necessarily linked in inheritance with the myopathy, though there is a tendency for this to happen.

There seems to be general agreement that the facio-scapulo-humeral type of myopathy is nearly always directly inherited (Niwa, Davidenkow and Kryschowa, Eulenberg and Cohn, and others). On the other hand, the neural atrophy of the Charcot-Marie-Tooth type was investigated from the point of view of inheritance by L. de Lisi, and he came to the conclusion that the disease is transmitted in all forms—dominant, simple recessive and sex-linked recessive.

An important piece of research work on a large myopathic family is published by Diehl, Hansen and V. Ubisch (1927). They recall that Weitz in his monumental work in 1921 collected together and analysed from the point of view of inheritance no fewer than 639 cases of the disease, and came to the conclusion that of these 62·4 per cent. were isolated cases; that in family groups about 50 per cent. of children were affected; that of all cases the proportion of males to females was 476 to 163; and that the malady was often transmitted by a healthy mother. They agree that if the ordinary dominant form of inheritance obtains, the only way in which to explain the occurrence of the isolated cases is on the assumption of the origin of a new mutation. They then analysed their own large family of cases and examined each member—myopathic or not—with great care, not merely for signs of muscular

defect, but for evidence of other structural departure from the normal They discovered that the family could be divided up into three groups—healthy, "Typ" and myopathic. The "Typ" cases had peculiarities of form common to one another but differing from the normal. They were small, thick-set and fat, with badly-modelled shoulders sloping in such a way that the breast appeared to be sunken. The other groups contained myopathics on the one hand, and "healthy" cases on the other. The latter as a rule were tall, thin and bony, with a straighter stance and good shoulder contour.

The genealogical table was then set out to show the three forms of cases—healthy, "Typ" and myopathic. They found that of 6 affected parents, each with a presumably normal mate, there were 34 children—16 healthy, 8 "Typ," and 10 suffering from myopathy. Postulating two factors (C and D), not linked but each derived from a separate parent, the expected result should have been 17, 8·5, 8·5, a correspondence so close as to confirm the postulate. From this and other considerations they came to the conclusion that in their family two separate mutants, C and D, must be present to give rise to a case of myopathy; and that the "Typ" was due to the presence of one such mutant, D. Thus their healthy cases might be of the genotype ccdd or Ccdd or even CCdd, whilst the "Typ" cases were those in whom D always appeared without the special factor C, their genotype being ccDd or possibly ccDD. If an apparently normal genotype who carried the C factor mated with a "Typ," myopathy could occur in the next generation in that a proportion of the F 1 group would be represented by the formula CcDd; the presence of both C and D in one genotype determining myopathy.

Diehl and his collaborators gave many reasons for thinking that the preponderance of cases in which males are affected and who derive this disease from a healthy mother, is artificial. They point out that for psychological reasons the existence of the defect is apt to be suppressed in the female, and that such disability as they may suffer may be no effective bar to house work, whilst the males all tend to come to light either at examinations for military service, or for failure in industry. Further, the tendency to suppression in the female results in a much larger number of myopathic females marrying than is the case in males. On this and other grounds they see no reason for believing that a sex-linked inheritance need be postulated.

It is noteworthy that in the allied condition of myotonia atrophica a form of inheritance had already been described by Fleischer which is

very similar to that put forward by Diehl and his collaborators. Fleischer found that in generations previous to that in which the explosive outburst of myotonia atrophica occurred, there were no cases of the fully developed disease; but that many and various evidences could be elicited of structural defects which could only be attributed to the inheritance of morbid factors. These defects were pre-senile cataract, failure of closure of the eyes during sleep and imperfect developement of certain muscles.

Minkowski and Sidler (1928) investigated all the cases of myopathy they could find arising in a population of 1,700 in a Swiss village. The village was to a large extent self-contained and the inhabitants rarely married outside their own community, so that a considerable degree of consanguinity existed between the various members.

There were no cases of idiocy, stunted growth, etc. In the case of the dystrophic families (10 families containing 13 cases of dystrophy), 10 pairs of parents had had 68 children, of whom 32 died in infancy; whilst in the earlier generation, when consanguinity was of still higher degree, only 26 out of 127 children died in infancy. Some cause other than mere consanguinity must therefore be causing this lack of viability, and similarly must be a cause of the muscular dystrophy. Although they found no case of myopathy in the direct ascendants of the affected cases, a careful inquiry revealed that in all cases each parent was a descendant of each of two particular family groups living in the sixteenth century. The explosive outbreak of the dystrophy could not be explained by the fact of consanguinity, which was closer in the previous generation; but it could be explained on the basis that the genotype of each parent contained a recessive factor derived from each of the stems R and H in heterozygous form; whilst the myopathic children were homozygous in respect of both recessive factors. They therefore concluded that the mode of inheritance was a Double Mendelian Recessive, and that the mutations giving rise to the disease probably occurred in the sixteenth century. There was no evidence of sex linkage in their cases; *formes frustes* and defects in the skeleton or musculature of relatives, do not appear to have been present.

Davidenkow and Kryschowa investigated the mode of inheritance, especially in a series of cases of the Leyden-Moebius type. They noted the frequency with which the collaterals of the mothers were affected and confirmed the earlier observation that a myopathic man may have a healthy daughter who herself may have a myopathic son. They looked for and found in many instances cases of skeletal or muscular defects in

relatives, such as herniæ, imperfections in the abdominal wall, sternum or vertebral column, ptosis and anomalies of the vegetative system.

Their general conclusion was that the disease is essentially dominant in its form of inheritance, and that the structural defects noted in the earlier generations, and particularly in the mothers and their siblings, were latent or abortive indications of the presence of the underlying genetic factor. These *formes frustes* were not specific for myopathy, many of them being defects not generally occurring in typical cases. They concluded that the same genetic factor could give rise to differing forms of neuro-muscular and skeletal defects in different individual members of the same family groups.

At this stage, and with so few adequate records of myopathics available, it is hardly possible to arrive at a final conclusion as to the mode of inheritance. Generally speaking, the numbers in each group are too small for the arithmetical methods of the geneticists to be applied with any degree of certainty, and the observations so far recorded are too discordant. Probably a clearer approach to the subject could be made if we separate out the groups of cases. Putting by themselves those families where the developed disease has occurred in each of several generations, and in which the inheritance is clearly of a dominant character, we find that they show certain characteristics in which they differ widely from the other groups; they tend to breed true to type, and are polymorphic only to a small degree; they tend to occur in females with a frequency only slightly differing from that in males and to arise at the same period of life (homochronia); they are only moderately disabling in their manifestation; and *formes frustes* are rare. This group of the myopathies will include most of the cases of the Landouzy-Dejerine type, and a few of each of the others (pseudo-hypertrophic, juvenile, Leyden-Moebius, Zimmerlin, and variants). On the other hand, the "isolated" cases, and those which occur in small numbers and often in one generation only, although they exhibit the same structural damage in the muscles, and often correspond closely to the forms of the other group in the regional distribution of the damage, tend to affect males far more frequently than females, to manifest themselves at all ages, are much more disabling in their intensity, and are associated with many evidences in their relatives of polymorphism, both of true myopathy and of abortive forms (*formes frustes*).

The careful work of Diehl, Hansen and Ubisch, and the equally painstaking records of Minkowski and Sidler, leave little room for doubt

that in their cases the disease factor was inherited in double form, and that it was the co-existence of two mutant genes in the genotype that gave rise to the myopathy. But it is clear that though each group of authors puts forward a form of inheritance postulating two factors, whose co-existence in a genotype is necessary for the manifestation of myopathy, the modes of inheritance suggested are not identical; in the former a double (dimeric) dominant is deduced, the corresponding chromosomes not being homologous; in the latter, a homozygous genotype is propounded, in which each of the pair of chromosomes carries both factors (i.e., a double recessive form of transmission).

At present it would appear that the varying forms of myopathy are not transmitted after any single mode, nor does it appear necessary to assume that the same mode of transmission shall be present if the disease is one *sui generis*. Dominance is a relative term, and all kinds of variations in its degree occur. In our own cases, and in a large majority of those published, the dominance only becomes manifest late in life, so late that it must have been wrongly regarded as recessive in our Case 118, had that one been examined as an "isolated" one. The degree of dominance of a mutant must to some extent be determined by the other thousands of genes present in the zygote in order that we may explain the heterochronia, whilst the rarity with which true polymorphism occurs in the larger family groups suggests strongly that it is in them always an identical mutation of the same gene, but that in other groups mutations, possibly allelomorphic, are responsible. As to whether a second specific mutant factor is present in all cases (so that a "combined action" is necessary to manifest myopathy) is a point that can only be cleared up by further research in the same careful way as that pursued by modern workers. In our own cases it is clear that if two factors are present they are linked together in the same chromosome, though Cases 66 and 136 suggest the possibility that the factor for myopathy has been lost in the one and for adiposity in the other.

In general the position may be summed up as follows:—

(1) In some cases one mutant only need be postulated.

(2) That the mutation is not always identical.

(3) That in some cases the mutant gene is so completely dominant that its presence is expressed in every genotype which carries it, whilst in other cases the mutation is fully recessive, and is only manifested in genotypes carrying the mutant in each of two paired chromosomes.

(4) The preponderance of the affection in males in the second group of cases (i.e., those whose inheritance is not clearly of a dominant type)

is so great that it is not yet possible to exclude the possibility that the mutant is sex-linked (i.e., has its locus in the X or female sex-chromosome).

(5) In some groups of cases the presence of two mutant but non-allelomorphic genes provides the best explanation of the origin of the disease, and this may occur either in homozygous or heterozygous form (CC DD or Cc Dd).

(6) New mutations may arise; such a primary change in the zygote is probably a rare manifestation, and does not account for more than a small number of the cases recorded.

Conclusion.

(*a*) *Clinical.* (S. Family.)

(1) A variant of myopathy, occurring in many members of a single family, is here described which passes through four phases: hypertrophic, pseudo-hypertrophic, atrophic and terminal, the last stage being associated with a distal atrophy of the upper extremities.

(2) Other clinical characteristics are early loss of tendon reflexes, late onset and slow progress; an almost constant association with adipositas universalis, and a relative absence of *formes frustes* and of polymorphism.

(*b*) *Inheritance.* (General.)

(1) A large and increasing body of evidence is available, which goes to prove that myopathy (muscular dystrophy) is determined at the birth of the ovum, and is derived as a factor or as factors inherited from one or both of the two gametes which form the zygote. In rare cases, a new mutation (variation in a normal gene) may arise and be the cause of the condition in the individual developed from that zygote, and be transmitted to his descendants.

(2) As to whether the effects of the mutant are manifested directly during the development of the individual, or indirectly through the endocrine glands, has not been established. The frequent association of myopathy with adiposity and other evidence of endocrine imbalance, may be interpreted on strictly genetic lines, the hormone disturbance being a secondary effect of the mutant.

(3) In those cases where microbic disease, trauma, overwork, etc., are antecedent in the history, they are merely factors which determine the onset or accelerate the progress of the disease in an individual who is a potential myopathic, i.e., a genotype carrying the mutant gene or

genes. Apart from the presence of such underlying factors, it is probable that the muscular dystrophy can never arise.

The Family Record.

The records given here are culled from various sources. Many—all the earlier ones—are abbreviated from notes supplied by older members of the family still living. The family name for the disease has been, not unnaturally, locomotor ataxia.

Where atrophy has been mentioned either as being present or absent in these notes, a reservation must be made on account of the goodly covering of panniculus adiposus which may to some extent mask diminution of size in the muscles, and which is so abundantly present in most affected members of the family. This reservation does not, of course, apply to atrophy of the intrinsic muscles of the hands. In Case 46, gross œdema of the feet and legs masks (1931) a possible atrophy of the tarsal interosseous muscles.

A few living members have been examined many times, but most of them have been examined once or twice only. In all, about 160 descendants of Case 1 have been examined. The first occasion was in 1922, when I had the assistance of Dr. E. Weston Hurst; the last was during 1931, when Dr. G. R. Bashford and Dr. E. J. Kerr helped me to continue the record.

In the main, for brevity, only positive findings are recorded. In all cases where tests were made, electrical reactions were of normal (not R.D.) type. In no case was any loss of size or power detected in the sternal half of the pectoralis major muscles, in the face or sternomastoids; the eye muscles and bulbar groups have been consistently normal. In no case was fibrillation seen, but the heavy layer of fat covering most of the affected muscles would have made it difficult to observe it, even if present.

In a few cases details are given of the size (by limb circumference) and power of muscles. The latter was estimated by putting the patient's muscles into active contraction against resistance by the observer, and a rough estimate was thus formed as to the power remaining; no accuracy in detail is claimed for the figures given.

At the time the earlier of these examinations were chiefly made, I was not aware of the observations of Diehl and his collaborators, so that the records of adiposity in other (non-myopathic) members of the family are imperfect. My recollection is that in those I have seen personally (about seventy in all) adiposity of abnormal degree is absent.

Cases.

1.—*Thomas S.*: Migrated from Leicester to Birmingham in 1776, where he founded a very successful business. Believed to have been born in 1749, and is known to have died in 1836. His will, made in 1835, mentions 11 children (8 sons and 3 daughters); in respect of 7 of them, it is not known whether or not they were myopathic, and they are omitted from the table.

Thomas S. was nicknamed "Ducky" on account of his gait. Was of powerful physique, had a long body and short legs. Had difficulty in getting about during his later years, and a specially constructed buggy was built for him with a very low step, so that he could haul himself into it. He had increasing paralysis of the legs up to the time of his death.

2.—*William S.* (son of Case 1): Born 1797, died 1871. Said to have been "shaky" for a few years before death, but was probably not myopathic. A photograph (about 1865) shows no atrophy of his hands. Was tall and well built, but not abnormally fat.

3.—*George S.*: Died at age 67, having been paralysed for many years. No details available. Is known to have had a family, but these cannot be traced.

4.—*Charles S.*: All records suggest that he was not affected. There are now alive various grandchildren and great-grandchildren of his; not all of those living have been interviewed. His son, Aeneas, died unaffected in 1906, aged 59, and his family of five sons and five daughters (aged 45 to 60) are alive and unaffected. No case of the disease is known to them as occurring in any of the descendants of Charles S., and his issue has been omitted from the table.

5.—*Thomas S.*: first became aware of the onset of the malady at about the age of 45, and, realizing its nature, became addicted to alcohol and died at 50, in 1859.

6, 7, 8 and 9.—All lived to middle age, married and had descendants. No myopathy.

10.—A female, became affected in middle life, and died at the age of 65.

11.—A female, became affected late in middle life. No details available.

12.—A male, first evidence of weakness at about 45 years of age. He was a powerfully built man who, in his youth, had performed feats requiring an abnormal amount of strength. He died at 70; was myopathic and adipose.

13.—A female, died at 74, having suffered from the disease for many years. Was myopathic and adipose.

14.—A woman, unaffected.

15.—Born about 1825. Was of Herculean strength and endurance; nicknamed "Hit-away Harry," as a boxer in his youth. Later, nicknamed "Harry the Rapp," on account of his stamping gait. He became progressively weak in the legs from the age of about 40, but lived to nearly 70. Myopathic (including hypertrophic stage) and adipose.

16 to 40.—None of these cases (some examined personally) show any myopathy.

41.—No disease.

42.—Myopathic and adipose. Died twenty years ago; not examined personally.

43 to 45.—Normal; no examination.

46.—A male, aged 72 on first examination in 1923, is the oldest living member of the family. Here the symptoms began at the age of 50 with painful cramps in the calves and in the lumbar region. Later a progressive

loss of power in the legs developed and during the last two years the arms and hands have become involved. Prior to the onset of his symptoms he had shown the Herculean proportions and capacity so typical of the family. He was by profession a furniture remover, and at the age of 30 could carry a piano on his back without assistance, and would work at his trade for twenty hours at a stretch. If a piece of string were tied round the arm when at rest he could snap it with ease merely by contraction of his biceps. He walked with the "peacock strut" characteristic of the affected members of this family.

On examination (1923) the clinical picture is one of an unusually well-built man, largely bedridden on account of great muscular weakness. There is no obvious wasting in the legs, the calf muscles being of average size but giving the impression on palpation of being more fibrous than muscular. The left vastus internus is much shrunken, and there is moderate atrophy in that of the right side; the main weakness is however in the ilio-psoas muscles. The feet are unusually short. The approximate strength of the anterior tibials is 25 per cent. and of the calf muscles 20 per cent. All the tendon-jerks are entirely absent.

The arms and fore-arms show no atrophy or hypertrophy, but all the intrinsic muscles of the hand are moderately atrophied, especially the first dorsal and other interossei. The pectoralis major is normal; the right biceps and triceps about 40 per cent. of normal and the right deltoid 20 per cent., although these last muscles are of normal size. The left arm is similarly affected, but here the power is about 60 per cent. of the normal. Neither scapula is winged. There are no arm-jerks. No fibrillary tremor was observed in this or in any other case.

The extensors of the neck and the sternomastoids are normal but there is no jaw-jerk.

Re-examined 1931, aged 80.—General health has remained extraordinarily good. The weakness of his legs has gradually progressed until he is now only able to walk with the aid of crutches. He can only rise from a sitting position with the aid of his arms and hands. Gets tired and knees sag after standing for a few seconds.

The left hand began to waste at the age of 70, the right soon after. Wasting is now evenly bilateral in the hands. Seven years ago he sustained a right Pott's fracture.

Muscles affected.—In hands, chiefly the first and second dorsal interosseous muscles; abductor brevis hallucis, slightly affected; flexor brevis hallucis, barely appreciable action; the hypothenar eminences are normal. Flexor muscles of the fore-arm very weak, so that there is dorsiflexion of the hand during grip. Pectoral muscles excellent on both sides. All shoulder-girdle muscles good, but the spinati are not so big as would be expected in one of his muscular development. Abdominal muscles fair. Erectores spinæ, thin. Extension of knee 20 per cent., extension of ankle 10 per cent., flexion of knee 20 per cent., flexion of ankle 10 per cent. Gluteal group 25 per cent., ilio-psoas 10 per cent.

Measurements.—(Maximum circumference). Fore-arm right $9\frac{3}{4}$ in., left $9\frac{1}{2}$ in.: arm, right $11\frac{1}{4}$ in., left $10\frac{1}{4}$ in. Biceps very weak. Triceps moderately weak. There is general failure of power below elbow, but no absolute loss.

Reflexes.—No arm-jerks elicited, no ankle-jerks, no knee-jerks, no plantar reflexes.

Circulatory system.—Shows chronic, gross œdema of both legs from the mid-leg downwards, pitting of 2 cm. Blood pressure 184/100. Rather softly acting heart, otherwise normal. Slight œdema of the loins is present.

47.—A male, now aged 68. A thin man, who has recently developed atrophy of both hands (mainly involving radial interossei and thenar eminences, leaving hypothenar muscles normal). No weakness of legs. No ankle-jerks present. The knee-jerks can be obtained on reinforcement. *Forme fruste* of myopathy without adiposity. See photograph (fig. 7).

48.—A man, believed to be unaffected. Died unmarried at age of 50.

49.—A female, born in 1856, now alive; began to have symptoms between the ages of 30 and 40. She had never possessed an abnormal degree of strength and the onset was painless, the patient merely noticing a tendency to fall over any slight projection, with subsequent difficulty in rising. During the last four years weakness in the arms has become a feature.

The lower limbs show an exactly similar condition to that in Case 52, except that the loss of power is even more marked (to about 30 per cent. of normal).

In the hands there is considerable atrophy in the small muscles, elsewhere there is but little. Power in the arm and fore-arm groups generally is subnormal and all the tendon-jerks are absent.

Myopathy; moderate degree of adiposity.

50.—A woman, died at the age of 64. Walked badly in her later years. Myopathic.

51.—A woman, aged 56. Began to be affected at 49. Adipose and myopathic.

52.—A male, has reached 57 years of age (1922). When 34 years old this patient suffered from a severe attack of acute rheumatism, and on rising from his bed noticed a marked weakness of his lower limbs which contrasted sharply with his previous muscular strength, which again was very much above the average. Unlike most of the other cases the onset here was unaccompanied by cramps and was indeed quite painless. He has not been aware as yet of any loss of power, though there is an early atrophy of the intrinsic muscles of the hands.

Examination shows considerable atrophy of the calves, the other muscles of the lower extremities being diminished in size to a less degree. The foot is short and Z-shaped and there is slight contracture of the tendo-Achillis. Muscular power is everywhere less than normal. The gait is similar to that described in Case 89. Moderate degree of adipositas universalis.

In the hands an early atrophy of the radial interossei and of the thenar

eminence is seen, but none is obvious in arms or fore-arms. Muscular power here is a little below the normal and the tendon-jerks are absent in both legs and arms.

Re-examined 1931.—Aged 66. Can just walk alone without any assistance. In all circumstances the patient keeps erect in walking. To get upstairs he uses his hands. Evidently his greatest loss of power is in quadriceps and ilio-psoas group.

Size of legs.—Now general atrophy. Right thigh 16 in., left thigh $16\frac{1}{4}$ in.; very thin calf, right 11 in., left $11\frac{1}{4}$ in. Dorsiflexion of ankle, right 10 per cent., left 15 per cent; flexion, plantar, right 10 per cent., left 15 per cent. Extension of knee, right 10 per cent., left 10 per cent. Hamstrings, right 30 per cent., left 30 per cent. Flexion of hip, left 5 per cent., right 5 per cent. Extension of hip, 15 per cent. Knee-jerks and ankle-jerks absent. No pseudo-hypertrophy. No power of flexion or extension of toes. Feet show tendency to Z-shaped contracture. All muscles are rather tough and hard. Normal range of movement at knees and hips, but only moderate at ankle. Slight contracture in normal position, so that flexion and extension are both limited.

Hands.—There is considerable loss of grip and a tendency to extension of hand on fore-arm during grip. There is considerable atrophy of interossei of both hands. Both arms of moderate power. Pectoral and shoulder-girdle muscles good.

Arm measurements.—Left 10 in., right 10 in. Fore-arm, left $9\frac{3}{4}$ in., right 10 in. Hand, left $8\frac{1}{2}$ in., right $8\frac{5}{8}$. Atrophy chiefly of first dorsal interosseus and abductor pollicis. Each hand tends to adopt the *main en griffe* position. All muscles have less power than their size would indicate. He cannot rise from the floor alone. No pseudo-hypertrophy. Myopathic and adipose.

53 to 56.—None now alive. All died between ages of 25 and 50. Believed to be unaffected but record uncertain. No. 55 died soon after birth of 118, and at the age of about 30.

57 to 59.—Believed unaffected. None now alive, not examined.

60.—Began to be affected at age 30. Died in infirmary where he had lain for twenty-two years. Had tumour of face (? lipoma). Myopathic and adipose.

61.—Discharged from Army with paralysis of legs in 1867; died 1884. Myopathy.

62.—Died in 1914. Used to have a "waddling gait," and "had to put his hands on his knees to get out of a chair." Myopathy.

63.—Had a waddling gait and the "S. tap" (clicking of the heels in walking). Died in infirmary in 1922 after years of paralysis. Myopathic.

64.—Was attacked at 25, and needed two sticks to get about. Died of cancer at age of 45. Myopathy.

65.—Required support to get about in later years. Often fell down when crossing roads, &c. Died of dropsy in 1892. Myopathy and adiposity.

66.—Died in 1908, aged 73. Was very fat, reaching 20 stone weight (280 lb.). Had no muscular weakness. Died of septicæmia. Adipose, not myopathic.

67.—Adipose, died of dropsy about 1900. Began to be affected in legs at age 60, and by age 63 could not get up alone from her chair. Age at death, 70 Adipose and myopathic.

68.—Died after many years of progressive paralysis at age 70, in 1913. Could not stand alone for years before death. Adipose (250 pounds) and myopathic.

69 to 79.—All normal.

80 to 83.—A series of children, nine in all, none of whom lived to puberty. Cause of deaths unknown.

84 to 88.—All normal.

89.—A man, born in 1874. The first symptom in this case was at the age of 42; when walking there developed a sense of constriction in the left calf which increased in severity until it became actual pain and the movement had to be suspended. At this time the left calf was considerably larger than its fellow. The pain recurred whenever walking was attempted for more than a few minutes and the calf gradually increased in dimensions. His medical adviser was consulted and eventually a radiograph of the limb was taken, which, however, revealed no cause for the swelling. The patient then visited a surgeon who diagnosed a subaponeurotic lipoma and undertook an operation for its removal. Nothing but muscular tissue was found and unfortunately none of this was removed for microscopical examination. Following the operation there was a progressive diminution in the size of both calves which later spread to the muscles of the thigh, and accompanying this a gradual loss of power. The pain became a less noticeable feature and only a dull aching in the lumbar region, when walking is attempted, remains. The arms are not affected. Here again the patient had previously possessed unusual strength and powers of endurance. He could, in his youth, perform feats at once the source of admiration and of despair to his acquaintances. He could raise a 56 lb. weight between the thumb and first finger of each hand. He could climb a flight of stairs with a sack of corn weighing 500 lb. on his shoulders. On one occasion he attended a fair where a performing bear was wrestling with his keeper, and in response to a challenge succeeded in throwing it.

Examination (1923) shows a well-nourished man of 49 years of age with a marked tendency to adiposity. The lower extremities are somewhat slender when compared with the rest of the body, and the feet are short. The maximum circumference of the leg below the knee is 15 in. as opposed to 17½ in. when he was at his maximum development. This bulk does not represent muscular tissue, of which but little can be detected, but is mainly due to fatty and fibrous tissue. There is considerable loss of power, especially in the peripheral part of the limb, but the small muscles of the foot are unaffected. The approximate strength of the various muscle groups is as follows: Extensors of thigh, 30 per cent., flexors of thigh, 30 per cent. Abductors of thigh, 60 per cent.; adductors of thigh, 30 per cent. Extensors of knee, 30 per cent.; flexors of knee, 30 per cent. Extensors of foot, 20 per cent.; flexors of foot, 20 per cent. Invertors of foot, 20 per cent.; evertors of foot, 20 per cent.

The knee-jerks and ankle-jerks are absent and the plantar reflexes flexor. There is no lordosis.

The patient stands with the legs far apart in order to maintain the upright posture. If the legs are approximated he sways backwards and forwards a few times and then falls. In standing, the knees are held rigid in a position of slight hyperextension, and the gait is waddling in order to enable the moving leg to be thrown forwards to clear the ground. The heel is first brought into contact with the floor with a sharp click, and the toes of the static leg are firmly flexed as the man moves forwards. As the result of this there is a callosity over the interphalangeal joint of each great toe. If the semi-conscious effort to keep the knee extended is relaxed, the leg doubles up, and the patient falls. Once down he cannot raise himself without the assistance of a chair or some similar object. He places his hands on the chair, draws up first one knee and then the other, and then with his feet widely separated raises his body with the aid of his arms, extends his knees, and once more regains the upright position.

He cannot walk upstairs without the assistance of his upper limbs.

The arms are throughout of large size and power, and the tendon-jerks here are present.

Re-examined 1931.—Aged 57. Walking has gradually deteriorated during the last ten years, and if he falls on his knees he cannot get up without help. At first he was able to get up with the aid of a post, but two years ago he had a bad fall on to his knees and sustained a right inguinal hernia. Recently he has been getting cramp in the thighs after sitting for a few hours. During the past three years there has been a considerable degree of wasting in both arms.

Nervous system.—Marked weakness was present in all the following muscles: Left anterior crural muscles to a greater extent than in the right, which were also weaker than normal. Hand grips definitely weak, wrist movements good, dorsiflexors of the feet very weak. Muscles of both hands equally involved. Atrophy affects chiefly the abductor indicis, abductor pollicis, thenar eminences and the opponens pollicis of each hand. Calf, left 14 in.; calf, right 14½ in. Sensory functions: tactile, pain, temperature and joint sensation are normal. Vibration sense absent in the legs. Co-ordination good. All tendon-jerks absent; abdominal, reflexes absent and plantars flexor. There is no weakness of any of the muscles supplied by the cranial nerves. Cholecystectomy was performed (two weeks previous to present examination) for acute cholecystitis.

This patient has three children, of whom the eldest and the youngest show an early stage of the disease (Cases 156 and 157). See photographs, figs. 4, 5 and 6.

90.—Aged 55, examined and found normal.

91.—A woman born in 1877; has noticed this year (1922) that she has some weakness in the legs. She cannot stand on the toes nor rise naturally from a chair, and she has developed the typical family gait. The calves are, proportionately to the rest of the body, enlarged. The left measures 15⅝ in. in

maximum circumference and the right $16\frac{3}{8}$ in., the former being the weaker. The ankle-jerks and knee-jerks are absent. She is markedly adipose, weighs 186 lb., height 5 ft. 1 in.

On re-examination in 1931: aged 54, weight 210 lb., height 5 ft. 1 in. Can still walk with the aid of a stick. In the arms the muscles are all very big, especially in the fore-arm, but are beginning to get weak. There is much panniculus adiposus. The only atrophy is in the 1st dorsal interosseus. Tendency to hyperextension of knees in walking; tends to fall backwards when standing and has to keep moving in order to keep erect. The weakest movements are flexion and extension of the hips, which are only about half normal power. Flexion and extension at knees nearly normal. Rising from chair is only possible either with assistance of her hand or a full swing of body forwards.

She has three children, the two eldest being in different stages of myopathy.

92.—Normal; not adipose. Aged 51.

93.—Died at 31. Neither myopathic nor adipose. Suffered from epilepsy.

94 to 101.—All these men, whose ages range from 27 to 44, are normal in appearance, and are not adipose. None show myopathic weakness. Tendon-jerks in all are normal.

102 and 103.—Normal according to report. Their present ages are 44 and and 37: neither has been examined.

104 to 107.—These four (eldest 33) are all said to be normal. None examined.

108.—A man, aged 31. Began to show weakness of hip muscle two years ago. Typical family gait. No leg reflexes. Moderately adipose; myopathy.

109 to 112.—These four, eldest 33, are said to be normal. Not examined.

113.—Woman, aged 41, examined, normal.

114.—Aged 39, normal.

115.—A man, aged 35 at first examination in 1921, left-handed, had pain in the thigh and calf muscles towards the end of his day's work. He has noticed no weakness but is a strong man who can lift four to five hundredweight with ease.

The legs show a remarkably good musculature with no sign of any disease except that the knee-jerks are absent. The arms again are of more than average development and here the jerks are present. He has five children, of whom the eldest alone (163) shows any abnormality.

Re-examined 1931.—Aged 45, is still in the hypertrophic stage. Calves, right $15\frac{1}{4}$ in.; thighs, right $19\frac{1}{2}$ in., left 19 in. All movements of ankle free and powerful. Power in all muscles of flexion and extension of ankles and knees about 120 per cent. Psoas iliacus, 90 per cent. Gluteal group, 95 per cent. Hands, full size and power. Knee-jerks, nil. Ankle-jerks, present both sides. Biceps-jerk, also just present. Triceps-jerk, absent. Arm measurements, right arm $12\frac{1}{16}$ in.; right fore-arm, $11\frac{1}{4}$ in.; left arm, 12 in.; left fore-arm, $11\frac{1}{4}$ in. There is a strong suggestion of true hypertrophy of both calves. No atrophy of pectorals. Musculature is far ahead of normal in

general size and power. The only failure of power is slight, in flexion of hip. In the legs there is definite hypertrophy. He is so far unconscious of any weakness. Myopathic and of moderate adiposity (see figs. 1, 2, 3, and 4).

116.—A woman of about 45 years of age. All reflexes normal. Moderate adiposity. No myopathy.

117.—A male, aged 34, has been affected for four years. He suffers occasionally from attacks of giddiness causing him to fall; in these there is a feeling of extreme heaviness in the lower limbs, during which they cannot be controlled by an effort of the will. On exertion he has severe cramps in the muscles of the calves and thighs.

Examination shows an apparently well-developed man, though not so Herculean in his proportion as some of his relatives. There is pseudo-hypertrophy in both thighs, but both knee-jerks can be obtained on reinforcement. The ankle-jerks are absent. No atrophy is present anywhere, although he says the muscular power is very definitely less than it was five years ago. The right vastus externus shows well-marked myotonic contraction on light contraction, and to some extent the vastus internus and rectus femoris share in this phenomenon. On strong contraction the rectus femoris goes into spasm similar to that seen in Thomsen's disease.

There is no lordosis. The gait is typical, and the patient rises from the prone position in the manner usually adopted by subjects of pseudo-hypertrophic palsy, though with much difficulty. The arms have a normal degree of power, but the tendon-jerks are absent. The sternomastoids are normal.

Re-examined 1931.—Aged 44. Weight 168 lb.; height 5 ft. 4 in. Gait substantially normal. Can rise from chair nearly normally. Muscles of legs above average size. Calves tougher than usual. No contracture at ankle.

Power.—Dorsiflexion of ankle, right 75 per cent., left 75 per cent. Plantiflexors, right 100 per cent., left 100 per cent. Knees, extension 100 per cent., flexion 100 per cent. Right hip, extension 40 per cent., flexion 40 per cent. Left hip, extension 50 per cent., flexion 40 per cent. Ankle-jerks and knee-jerks are absent.

In the arms and shoulder-girdle, all muscles are about normal in size and consistency. Power in arms normal throughout. No atrophy of hands. Muscles of neck all normal. All tendon-reflexes absent in arms and legs.

Measurements.—Right arm $12\frac{1}{2}$ in., left arm 12 in. Right fore-arm $11\frac{5}{8}$ in., left fore-arm $11\frac{1}{4}$ in. Right calf 13 in., left calf $13\frac{3}{8}$ in. Still has tendency to myotonic contraction of thigh muscles but no fibrillation was present. Adipose and myopathy. Tendency to myotonic contraction.

118.—A man aged 40 who was first seen in consultation in 1923. Always big and strong in his early manhood. Took a commission in the Great War (1915); could march twenty miles a day with ease at commencement, but when he left the Army in 1919 used to get pains in calf muscles and to tire after a few miles: gradually less capable of long standing and walking. In 1923, all muscles much above normal size, but in legs of barely normal power. Extension of knees and flexion of hips definitely weak (about 60 per cent. each)

No reflexes at ankle, knee or in arms. No wasting anywhere. Adipose (weight 194 lb.), height 68 in. Found to have hyperpiesia and chronic nephritis. Muscular power in legs gradually declined and atrophy of the muscles of the hands began in 1927. Died at age of 48, of heart failure, in January, 1931. Fragments of muscle were obtained (see further description, and photo-micrographs of muscle sections in Plates I and II.)

119.—Died young. No history available, but believed by brother to have been normal.

120, 121.—Two sons aged 60. The second normal on examination: the first reported to show no sign of myopathy, but is fat; has been a boxer, age now 42.

122.—Man, aged 56; examined, normal.

123.—Died at age 5, in 1887. Could never walk. Could "only riddle himself along the floor," i.e., was presumably a "buttock walker." No other facts available.

124 to 126.—Three women, aged 47 to 60, all examined and found normal.

127.—Died young, unaffected.

128.—A woman aged 43; examined, found normal.

129.—Died in childhood.

130.—Born in 1886. Began to walk badly at age 15, married her cousin (not of the S. family), emigrated to America. Has been bedridden for ten years. Has a daughter who is said not to be affected. Myopathic and probably adipose.

131.—A man of 73 (born 1858). Began to notice weakness of legs at age 57, gradually worse since. Legs now severely affected, but can still just walk with the aid of two sticks. No affection of hands. No tendon-jerks. Myopathic and adipose.

132.—A woman, who died at age 35, unaffected. Not examined.

133 and 134.—Died at ages 50 and 40, neither known to be affected. Not examined.

135.—A thin man, aged about 50, no evidence of disease. Reflexes normal.

136.—A thin woman, aged 47. Began to have difficulty in walking at 11 years of age. Never hypertrophic, no pseudo-hypertrophy. Gradually increasing weakness in legs; no pain at any stage. First seen in General Hospital, Birmingham, 1916. Weight then 98 lb., height about 5 ft. 1in. Had then atrophy and weakness of severe degree in all muscles of hips, thighs and legs. All jerks absent. Diagnosed as case of peroneal atrophy (Charcot-Marie-Tooth). Seen again 1923, and re-examined 1932. Atrophy more advanced in lower extremities, but no single muscle entirely paralysed; average power 10 per cent. to 30 per cent., flexion of hips being weakest. Now getting atrophy of radial group of intrinsic muscles of hands (not in hypothenar group). Can still get about with crutches. Myopathy; no adiposity.

137.—Died at age 9; no myopathy.

138.—Died at age 19; no myopathy.

139.—Died young.

140.—Three other children, died in infancy. No myopathy.

141 to 150.—None affected. Several were examined in 1921, none re-examined. No record of adiposity.

151 to 155.—None myopathic or adipose. All now in middle life.

156.—Male, aged 25. Of moderate muscular development, not particularly adipose. No symptom of weakness. Knee-jerks and ankle-jerks are all absent, even on reinforcement. Incipient myopathy.

157.—Female, aged 19. Of unusually fine muscular development (true hypertrophic type). No weakness, but all tendon reflexes absent in lower extremities. See further description in text ("Hypertrophic stage").

158.—A female, aged 21. Since an attack of tonsillitis at the age of 12, the patient has suffered from a sudden giving way of the knees, especially when she is fatigued, which prevents her from running, and in consequence of which she was made goalkeeper in her hockey team. There is no pain in the muscles. The frequency of these falls has increased during the last two years, and they may occur three times in one day. She has difficulty in ascending stairs and is liable to trip over any slight elevation, such as a doormat. About the age of 14, and again recently, she suffered from "fainting attacks" associated with a "far-away" feeling and lasting a few seconds at a time. These sometimes recur five times in one day and then not again for a number of days. Last year, following an attack of gastritis, the muscular symptoms became more severe.

In height the patient is 5 ft. 9 in., with weight constant at 131 lb. There is no wasting of muscles but the foot tends to be Z-shaped, and there is a slight contracture at the ankle, in spite of which the foot can be voluntarily dorsiflexed beyond a right angle. There is no lordosis.

The measurements of the limbs are as follows:—

Calf (maximum), right 14 in., left 14 in. Thigh margin (6 in. above upper border of patella), right $17\frac{3}{4}$ in., left $17\frac{5}{8}$ in. Fore-arm (maximum), right $9\frac{7}{8}$ in., left $9\frac{5}{8}$ in. Arm (maximum), right $9\frac{1}{8}$ in., left $9\frac{3}{4}$ in.

Muscular power is approximately as follows:—

Plantar flexion and dorsiflexion of foot, right 60 per cent., left 60 per cent. Quadriceps, right 20 per cent., left 20 per cent. Ilio-psoas, right 50 per cent., left 50 per cent. Hamstrings, glutei and arm muscles, normal. The knee-jerks are both absent, as is the left ankle-jerk. The right ankle-jerk appears feebly on reinforcement. The arm-jerks are normal.

In this case it was possible to ascertain the electrical reactions of the muscles. There exists a general diminution of the response to faradism, while to the galvanic current there is a normal sharp contraction.

In walking there is the same hyperextension at the knee seen in the other cases, and the girl walks upstairs with knees rigid and with assistance from the hands and arms.

Re-examined 1931.—Aged 29. Height, 5 ft. $8\frac{1}{2}$ in. Weight 176 lb.

Chief weakness is in the ilio-psoas group, which is reduced to 15 per cent. Extensors of the knee are gradually getting worse, and she cannot walk

upstairs or cross knees without the aid of hands. Glutei normal; adduction and abduction at the hips diminished but not greatly so. Erector spinæ strong. No lordosis. Muscles of the shoulder-girdles and the first dorsal interosseus are normal. Ankle-jerks and knee-jerks absent. Myopathy; adipose.

159.—A male, aged 15, shows no abnormality save that the ankle-jerks are present only on reinforcement.

Re-examined 1931.—Aged 23. Has played Rugby football regularly. There is a tendency to hyperextension at the knees with some projection of the calf backwards.

Calf measurements.—Right 15½ in., left 15¾ in. Knee-jerks and ankle-jerks present on reinforcement. Probably no myopathy.

160.—A boy, aged 13 (in 1921). Small build, normal in all respects. Re-examined in 1931, still fully normal; no adiposity.

161.—A boy, aged 12. Has mitral regurgitation. Of under average build. No sign of myopathy.

162.—A normal boy, aged 18, average build; reflexes normal.

163.—A girl, aged 13, no weakness; has complete absence of knee and ankle jerks. No adiposity.

164 to 166.—Three normal children (ages 10 to 14). Reflexes present in arms and legs.

167.—A baby, aged 4, rather fat, all jerks normal.

168.—A baby, aged 2. Deaf and dumb. Normal reflexes.

169.—A man, aged 22. No weakness. All reflexes normal. Very thin.

170.—A boy, aged 16. Average build, rather thin, normal throughout.

171.—A man aged 20. Has mitral stenosis. No loss of reflexes or muscular weakness.

172.—Girl, aged 19. Average build, normal reflexes.

173.—Girl, aged 15. Muscles above average size; has no biceps, triceps or supinator reflexes, but knee and ankle reflexes normal. Probably myopathic.

174.—A boy, aged 11. All muscles of lower limbs above average size. Knee-jerks just present, arm-jerks absent. Not adipose. Probably myopathic.

175.—A girl, aged 4. No abnormality detected.

176.—A baby, aged 12 months. All reflexes normal.

177.—A girl, aged 18. Has infantile hemiplegia of light degree, with Jacksonian epilepsy. Reflexes present. Thin, no myopathy.

178.—Not seen, reported normal.

179.—A normal man. No adiposity, no myopathy.

181 to 186.—All examined, normal.

187 to 196.—All normal except 188: a youth who is deaf and dumb (congenital); see text.

197 and 198.—Ages 52 and 30. Examined, normal.

199.—A man, aged 52. Early atrophic stage. Began to show weakness at about age 45. Now has to use his hands to rise from a chair. Hands normal. Reflexes absent. Adipose and myopathic.

200.—A man, aged 37. Adipose, weight 224 lb. Examined, no evidence of myopathy. His father "thinks he will become so because he is fat."

201 and 202.—Examined, normal.

203.—A woman, aged 48. Difficulty in walking for last twelve months only. Adipose, myopathic.

204 to 208.—All adults (ages 27 to 38); all examined, normal.

209.—A young woman, aged 22. Thin: has no knee-jerks or ankle-jerks, but no evidence of weakness. Probably myopathic, no adiposity.

210 to 242.—Most of these, all adults, have been examined and found normal. No report of weakness in the others.

243 to 281.—Most of them have been examined. Ages range from babyhood to 25. All presumed normal; no case found with absent reflexes or weakness.

282 to 284.—Three babies. No examination.

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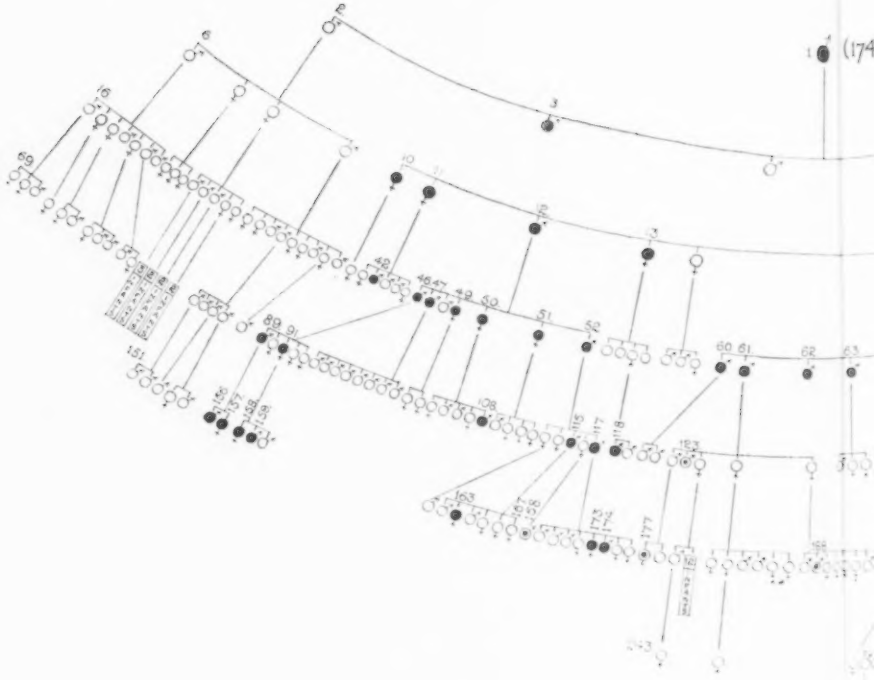
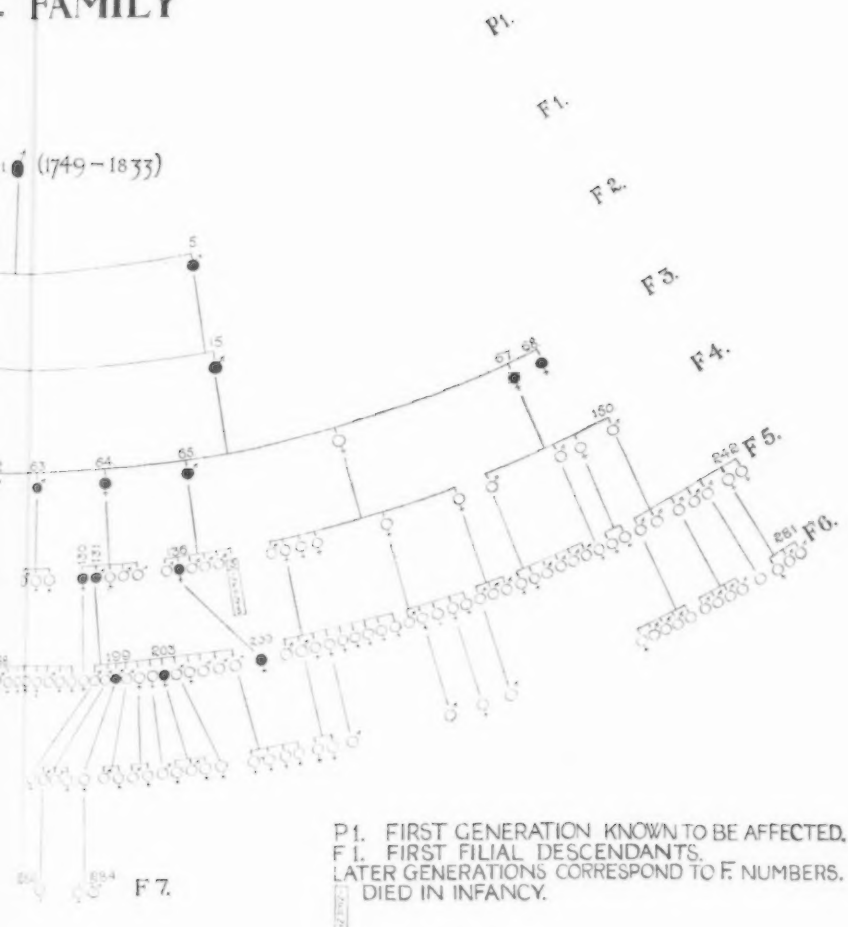


○ HEALTHY
● MYOPATHY
◉ DOUBTFUL CASES (SEE TEXT)

. FAMILY

(1749 – 1833)



P1. FIRST GENERATION KNOWN TO BE AFFECTED.
F1. FIRST FILIAL DESCENDANTS.
LATER GENERATIONS CORRESPOND TO F. NUMBERS.
DIED IN INFANCY.

FAMILIAL PERIODIC PARALYSIS. A DESCRIPTION OF SIX CASES OCCURRING IN THREE GENERATIONS OF ONE FAMILY.

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I.—Introduction.

II.—Description of Cases.

III.—General Description of the Disease—

(1) Ætiology.

(2) Pathology.

(3) Symptomatology and Course.

(4) Diagnosis.

IV.—Discussion

V.—Summary.

I.—Introduction.

The recognized features of the disease we are about to consider are the occurrence of periodic attacks of flaccid paralysis of comparatively sudden onset, without obvious cause, with diminution or loss of electrical excitability in the muscles of the affected limbs and absence of the deep reflexes. The degree of paralysis varies in different attacks from a partial affection of one limb to complete paralysis of all the muscles of the trunk and limbs, with the occasional involvement of certain muscles innervated by the cranial nerves. Variation is also shown in the duration of the attacks as these may last from a few hours to three or four days, while in exceptional instances death has occurred at the height of an attack.

A case of periodic paralysis reported by Cavaré in 1863 appears to be the first record of this condition in the literature. In 1885, Westphal and Oppenheim gave a detailed description of an isolated case, and later in the same year Goldflam described the familial nature of the disease. Since then descriptions of cases have appeared at intervals, the most notable being a series described by Holtzapple, in America, in which seventeen cases occurred in four generations of one family. In this

country Singer and Goodbody in 1901 were the first to describe a case of familial periodic paralysis, while later in the same year Buzzard described three cases, and Mitchell, in 1902, gave a description of a similar number. Since then, however, although occasional isolated cases have been recorded, I have been unable to find the records of cases occurring in more than one generation. Since the end of last century no advance has taken place in our knowledge of the disease, which still remains of extreme rarity, as altogether only about two hundred odd cases have been reported in the literature.

As in migraine, which has some points in common with familial periodic paralysis, one encounters insuperable difficulties in investigating the attacks, as these do not occur during the period of physical and mental rest with regular simple meals associated with residence in hospital. Particularly is investigation impeded from a biochemical point of view, for which it would be necessary for the patient to be on a diet of fixed composition in order to determine any variations preceding and during the paralytic attack.

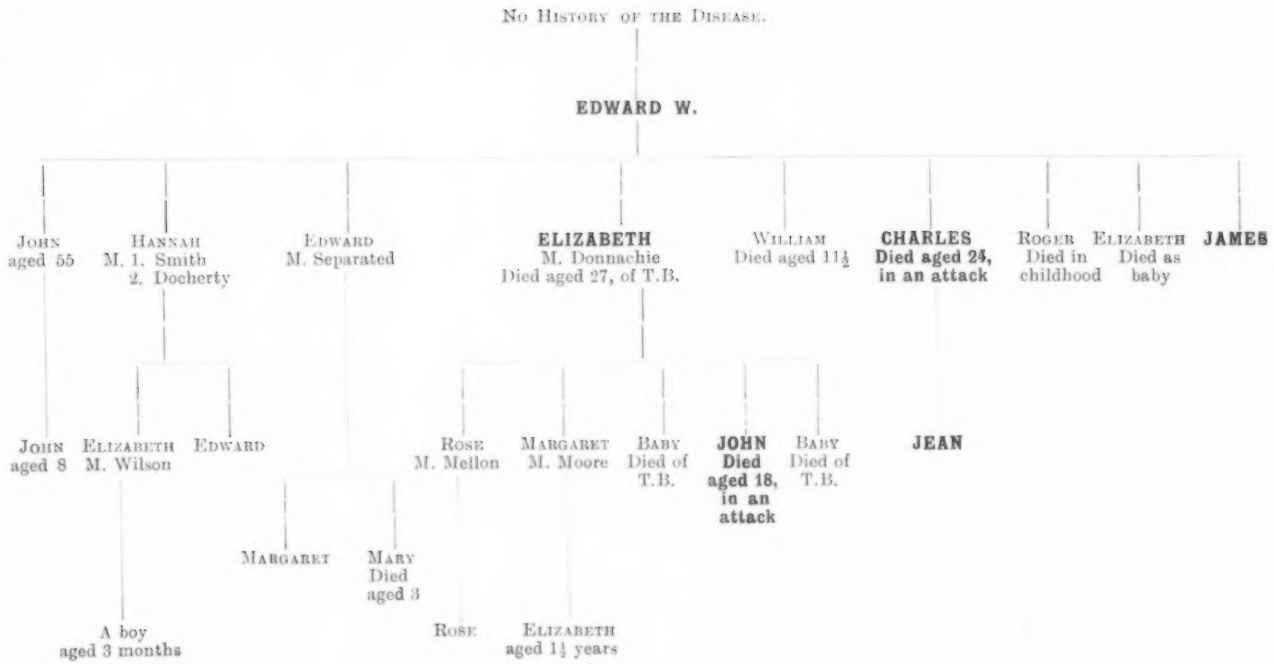
In the family which I have investigated, there has been difficulty in inducing those affected to come into hospital when paralysis supervenes, as their familiarity with the course of the disease has caused them to refuse hospital treatment unless an attack was aggravated by some co-existing condition. Even in the case of two members in whom a fatal issue occurred at the height of an attack, the family doctor was not even called in before death took place, as the course, prior to the incidents which precipitated sudden death, did not alarm the relatives.

II.—Description of Cases.

The paralytic attacks of three members of this family have not personally been observed by me, but the features of their attacks as reported to me are so similar to those experienced by the other members of the family that I have only remarked points in which they show any interesting differences.

In all those affected the paralysis was of a flaccid nature with the absence of the deep reflexes, and in no member of the family has there been any evidence clinically or serologically of a syphilitic inheritance.

(1) Edward W.: The first member of the family known to suffer from the affection lived to the age of 72 and died apparently from no definite illness, but just "old age." His attacks of paralysis were typical of those observed in the remainder of his family, but for fifteen years before his death he was free from attacks. He was an iron planer by occupation and an otherwise healthy man,


No History of the Disease.
EDWARD W.
John aged 55
Hannah M. 1. Smith 2. Docherty
Edward M. Separated
ELIZABETH M. Donnachie Died aged 27, of T.B.
William Died aged 11½
CHARLES Died aged 24, in an attack
Roger Died in childhood
Elizabeth Died as baby
JAMES
John aged 8
Elizabeth M. Wilson
Edward
Rose M. Mellon
Margaret M. Moore
Baby Died of T.B.
JOHN Died aged 18, in an attack
Baby Died of T.B.
JEAN
Margaret
Mary Died aged 3
A boy aged 3 months
Rose
Elizabeth aged 1½ years

and had not suffered from migraine or digestive troubles. As will be seen from the family tree he had nine children. His attacks commenced during the night and were foreshadowed by stiffness in the limbs, while the duration of each seizure varied from a few hours to three days. On one occasion he was paralysed on wakening in the morning at 6 o'clock, but had recovered so far as to be able to go to his work at 9.30 the same morning. Of his nine children, three died in infancy and three suffered from the disease.

(2) Elizabeth W. was the second of the original Edward W.'s nine children. Her attacks were similar to those which affected the other members of the family and commenced at the age of 18; she never suffered from any very severe attacks, the majority in her case being of the partial or abortive type, and she was never confined to bed for more than one day. She was married at the age of 19 and had four children, the second youngest of whom also suffered from the disease.

She died from pulmonary tuberculosis at the age of 28.

She was never seen by me and my information regarding her was obtained from her brother, James W., who also suffers from the disease, and therefore appreciates the points on which information is required. He informed me that her attacks had been less frequent and severe for some time before her death, and that the latter was in no way associated with one of the periodic attacks of paralysis.

(3) Charles W.: The attacks made their appearance at the age of 18 and though generally typical of the disease were more severe than those of his father in that speech was usually much affected, so that he was at times difficult to understand, and difficulty in swallowing was also present during the period of paralysis. Further, his attacks were more frequent, occurring two to three times a week and occasionally lasting forty-eight hours or longer, while emotion and exhaustion were in his case common exciting causes. He died at the age of 24 in an attack. On this occasion on wakening during the night he had felt an attack coming on and had risen from bed and "walked it off." On the following day, however, it recurred at 3 p.m., complete paralysis resulting with marked affection of speech and difficulty in swallowing. On the following day when his condition showed no improvement he was given a large dose of castor oil. This would not "go down" and some passed into the larynx, causing him to cough and choke and, so great was the weakness of respiration, that death ensued. This member of the family suffered from bulimia on the day preceding an attack and occasionally vomited clear mucoid fluid during his period of paralysis. His marriage was an unhappy one and his domestic life was one of disharmony; moreover he was wont to get his feet wet and this, and the cold at his work, were considered by him to be an exciting cause of the attacks.

(4) James W., is a butler. He was never robust, but on the other hand has had no definite illnesses. From the age of 6 years he suffered from periodic bilious headaches. When these occurred they were present on wakening in the morning and persisted all day until he went to bed at night. Vomiting occurred with some of the attacks of headache and this gave a certain amount of relief. These headaches occurred as a rule once a week and on many occasions were

so severe that he was unable to go to school. During these attacks he felt "poisoned" and unfit for anything until vomiting occurred or he went to sleep. There was no noted associated disturbance of bowel function. These periodic headaches persisted up till the onset of the attacks of paralysis, but disappeared within a year of the first of these attacks and have not since recurred. The first attack of paralysis occurred at the age of 18, and the next after a fortnight's interval; thereafter there was one attack a month till he was aged 23, when their frequency increased to once weekly.

He believes that cold and dampness of the feet predispose to attacks, but excitement and worry coupled with exhaustion appear to be factors of more importance. As is the case with many sufferers from migraine, he often feels exceptionally well on the day preceding an attack, and a voracious appetite coincides with this feeling of well-being; this was so marked that the other servants used to warn him when they noticed his exceptional appetite that he would be off duty the following day. If after a strenuous and worrying day culminating perhaps in a dinner party he had a meal late at night, which on such occasions usually consisted of rich food, an attack was almost certain. His longest attack, which lasted for four days, followed such a sequence of events, and during that period on being carried to stool two evacuations of the bowels took place.

He prefers sweet articles of food to meat, and is of the opinion that a meal which consists largely of protein, especially if consumed late at night, is likely to be followed by an attack.

In this case warning of an attack consists of stiffness of the limbs with a desire to stretch and move them, and such prodromata may precede the attack by two to three hours. However, unlike other sufferers from this paralysis, he has been unable to walk off an impending attack, but he has had on occasions short attacks followed after a few hours by a relapse; thus he was wakened at 3 a.m. with an increasing or complete paralysis, from which he had recovered by 3 p.m. the same day, and he has been able to do his ordinary work thereafter till bed-time, but during the following night the paralysis would recur and last for a similar period the next day; such relapses, however, have never occurred on more than two successive days.

Although in the majority of the attacks the paralysis has involved all the limbs, in a few instances the legs only have been affected, and still less frequently the arms alone have been involved.

The transition from severe paralytic attacks to minor abortive forms has been present for the last five years and coincides with a period of unemployment and accordingly with freedom from the long hours, rich food and strain of his occupation which previously appeared to be factors predisposing to attacks.

This patient is a small spare man of 5 ft. 4 in. in height and weighs 7 st. 6 lb.; his expression is habitually anxious and worried and he states that he has always had a sallow complexion. He is, however, well proportioned and there are no stigmata of degeneration and physical

examination revealed no evidence of any other organic disease. A fractional test meal demonstrated no free hydrochloric acid in any specimen up to two and a half hours after the gruel, and further evidence of inefficient digestion was obtained from the fact that digestion of starch had failed to take place throughout the same period, although the motility of the stomach appeared to be within normal limits. The Wassermann reaction was negative in both the blood and spinal-fluid and the latter showed otherwise no abnormality.

In the complete paralytic attacks the electrical responses to the faradic current were lost and were much weakened to galvanic stimulation, but in the minor abortive seizures which have succeeded the severe attacks during the last five years no abnormality of the electrical reactions has been noted. The basal metabolic rate was estimated on one occasion in the interval between attacks and the reading obtained was −3·5.

The minor attacks of recent years have been characterized by stiffness and numbness affecting one or two limbs, sometimes with a temporary paresis of a few hours duration, and with these there has been no gastro-intestinal or other general disturbance which has attracted his attention. In the major attacks his skin bas been usually pale and cold during the period of the seizure, but, as recovery commences, this has been succeeded by flushing and warmth of the skin with often obvious sweating.

(5) Jean W. This girl, now aged 23, is a daughter of Charles W., in the second generation of the family, who died during an attack of the disease. She was a normal full-time baby and was breast-fed for a year. At the age of 8 months she had "catarrh of the stomach" which was successfully treated, and she thereafter had no digestive complaints, but she has always suffered from constipation. After the age of 17 years she began to be troubled with periodic headaches which were always present on wakening in the morning, and thereafter increased in intensity during the day. These headaches were associated with a feeling of lassitude, vertigo and nausea, but vomiting did not occur as a rule and there were no visual phenomena. When the headache is near its acme she becomes very white and then there is frequently also a "cold sweat." At this stage there is usually a desire for fresh air, her respirations are deep and of a sighing nature, and she wants the windows in the room opened wide.

The first paralytic attack occurred in her nineteenth year when she was coming home from school. Her clothes had been soaked while going to school and while at work there she had felt stiff, but on leaving school she had to be helped on to the car as her legs were weak and uncertain. On reaching home three-quarters of an hour later she was quite unable to walk out of the car and had to be carried home.

The arms were slightly stiff, but there was no loss of power in them, neither was there any bulbar or sphincter symptoms. This attack passed away completely in about three hours.

The second attack occurred about three months later. It commenced

during the night about 4 a.m., when she awoke and called for assistance as she had a feeling of malaise and all her limbs were stiff. After having her limbs moved and rubbed she was able to go to sleep again, but woke at 7 a.m. unable to move any limb, but without difficulty in swallowing or breathing. The paralysis persisted for three days with no variation in degree and then gradually passed off. During its presence, although she was able to micturate on being supported on a stool once a day, presumably when the bladder became distended, no movement of the bowels took place until some hours after the attack had passed off. The next attack occurred after an interval of five months, when one morning on rising she was conscious of nausea and vertigo, which persisted after breakfast, while she was doing her usual domestic work, and even increased in degree. About 11 a.m. she went into the scullery to do something and while there was seized with vertigo and fell; she is said to have been unconscious for ten minutes and thereafter was found to be unable to move any limb, so was sent into hospital.

The sphincters functioned normally and there was neither dysphagia nor dysarthria. The paralysis persisted until she went to sleep, but she had completely recovered by the morning, although a sensation of stiffness persisted. Her condition was diagnosed by the house physician as hysteria.

Two months later another attack occurred. She had been out shopping in the afternoon after having done her usual domestic work in the morning, and as it was necessary for her to walk some distance she came home feeling rather tired. She was resting by the window when she felt her left hand stiff and this stiffness fairly rapidly affected in turn the rest of the arm, then subsequently the legs and then the right arm, along with weakness in the legs and also weakness of the left arm, necessitating assistance in getting her to bed. The legs became so much involved that she could not move herself in bed, and this weakness persisted until she went to sleep, but had passed away as before when she woke in the morning.

The next attack occurred three months later. On the preceding morning she had wakened with a headache, and had felt "out of sorts" and sick all day: she had cheese and toast with tea for breakfast, and for dinner at 2.30 p.m. she had Irish stew, potatoes, and a cup of tea. Her headache thereafter gradually disappeared, but she had no food at all during the remainder of the day and was out from 7 to 9.30 in the evening doing a message, and as the month was December she returned home feeling very cold. While sitting in a chair after her return she felt her right hand becoming numb and saw that it was slightly swollen. She was unable to move the fingers properly, and when she was going to bed at 10.30 p.m. she was unable to raise the left arm and required assistance in undressing. She slept well however, but on wakening at 7 a.m. she was unable to move any limb, sit up or raise her head from the pillow. She was able, however, to speak and swallow normally, and passed a large quantity of urine, but the bowels were confined. When seen by me at 11 a.m. the left hand was swollen, but no true œdema was present. She was unable to move any of her limbs and these, though not spastic, showed preser-

vation of muscle tone. She was still unable to raise herself in bed or move her head, but the respiratory muscles were functioning apparently normally, and there was neither dysphagia, dysarthria, or affection of any other cranial nerves. The tendon reflexes were not elicited, and the electrical reactions of the muscles while the paralysis was complete showed no response to either the galvanic or faradic current. She was pale, but there was no cardiac dilatation or arrythmia, and the blood-pressure was 120 mm. Hg. systolic and 80 diastolic. Two hours later when recovery was commencing, she was still unable to move the left arm, but all movements were possible in the right, and she could move her head and sit up in bed. Voluntary movement was still impossible in the left leg save for a slight amount of flexion of the toes and foot, and on attempting to move this limb passively one was conscious of stiffness of the muscles controlling the hip- and knee-joints. In the right leg, although voluntary movement was possible in all groups of muscles, power was still much impaired. Three hours later she was able to walk and to use both arms though power in all the limbs was still below normal. The swelling of the left hand persisted for three hours more.

At the height of the attack there was no suggestion of any sensory impairment, and no paræsthesiæ apart from the usual feeling of stiffness, which lasted for the remainder of the day. The following morning she felt in her usual health, power was completely regained and there were no paræsthesiæ. During this attack she did not pass urine or defecate, but the bladder was not unduly distended even when complete power had been regained in the afternoon.

In her next attack she awoke at 5 o'clock one morning feeling her limbs stiff and weak, but went to sleep to waken again at 7 a.m. unable to move any limb or sit up, but able to move her head, speak and swallow normally. This attack though generalized was of short duration and she had gained considerable power by 11 a.m. and was able to walk and feed herself by 1 p.m. On the previous day, in addition to her usual work, she had scrubbed a floor and had felt very tired in the evening.

As a rule in the attacks which have a general distribution recovery commences in the legs before the arms and in the proximal muscles of the arms before those distal, but occasionally the intensity appears to have a hemiplegic distribution or one side of the body recovers before the other.

In addition to the general attacks which have been occurring at increasingly shorter intervals since the age of 18 this patient has had numerous minor or abortive attacks. These consist of transient attacks of stiffness, or of stiffness associated with some muscular weakness and may be only experienced in one limb, or in both legs or arms, or more rarely may show hemiplegic distribution. They may last from a few minutes to half an hour and are not associated with nausea, headache or digestive disturbance, and may occur several times in one week. She is convinced herself that cold and dampness predispose to attacks but does not connect them with exhaustion following excessive work or other cause, and the periodic headaches from which she suffered along with nausea

have tended gradually to disappear since she began to suffer from the paralytic attacks.

Her most recent attack was associated, and perhaps excited by, an attack of acute bronchitis and arthritis with pyrexia which for several days was about 102° F.

She had been ill for four days before coming into hospital, and for the last three of these she had been paralysed in all her limbs, and was unable to turn herself, sit up in bed, or even to raise her head from the pillow. She was thus on admission to hospital, and the deep reflexes were absent in the arms as well as in the legs.

A small measure of recovery took place within twenty-four hours, aided possibly by much application of heat, and although some slight movement of the arms was now possible she was unable for a further period of four days to use them for feeding or performing her toilet, while for the same period she remained unable to move in bed or even raise her head. Thereafter within twenty-four hours power was gradually but completely regained. In this attack complete recovery was much longer in taking place than in any other of my patients, and improvement was only noted when the acute bronchitis and fever were lessening. This suggests that the disturbance of metabolism associated with the pyrexia of her infection may have aggravated and maintained the intoxication, which I believe precedes and determines the paralytic seizures.

Breathing was much embarrassed during her first four days in hospital, and more so than appeared to be proportionate to the degree of bronchitis. Her cough was weak and ineffective, expectoration was carried out with difficulty, while the accessory muscles of respiration were in action during this period. Her voice also was more weak than normal, but there was no complaint of dysphagia; however, at the time of the pyrexia she was having no solid food with which difficulty in swallowing might have been made manifest. Her respiratory difficulty gave rise to some anxiety during this period, especially as her father had died in a paralytic attack from a spasm of coughing exhausting the weakened respiratory muscles.

During this attack urine was passed only at lengthy intervals, sixteen to twenty-four hours, when the distension of the bladder formed a sufficiently strong stimulus to promote evacuation, but the bowels moved normally following the administration of laxatives. Although no dilatation of the heart was noted, the pulse remained more frequent than was proportional to the pyrexia and respiratory rate, while the cardiac sounds, though pure, were of very poor quality.

During this attack an electro-cardiographic tracing taken at the time of complete paralysis showed no abnormality.

This patient had suffered from attacks of increasing frequency and severity since their onset five years ago. For the last year the knee-jerks have been absent, and for the last five or six months it has also been impossible to elicit the ankle-jerks, while the reflexes in the upper limbs are now all sluggish.

Moreover the muscles of the calves have now on palpation a firm, fibrous consistence similar to that found in some of the muscular dystrophies, but there is no obvious atrophy, and between attacks I have not been able to demonstrate any loss of power, although she herself says that her legs are easily tired.

A fractional test meal performed a year ago in the intervals between attacks showed a subnormal amount of free hydrochloric acid in all specimens, and even at the end of two and a half hours there was no evidence of starch digestion. I have never found any cardiac dilatation in any of the attacks which I have personally observed, but in one attack in her home, in which after being carried to stool she was subsequently placed in the chair by the fire, syncope occurred. Apart from her last and most severe attack in which acute bronchitis co-existed, there has been no evidence of involvement of the cranial nerves. The Wassermann reaction was negative in the blood and spinal fluid, and latter otherwise showed no abnormality. There was no stigmata of degeneration, but she is of small stature although well-proportioned like the majority of the members of her family.

Owing to the duration of her attacks it was possible with this patient to place her on a fixed diet and to estimate the distribution of the urinary nitrogen in collections over periods of twenty-four hours, both during a period of normal health and in a paralytic attack. The results obtained were as follows:—

	Total N	Ammonia N	Uric acid N	Creatinine N	
				Total (including creatine)	Preformed
Normal period	6·66	0·259	0·100	—	0·217
Abnormal period ..	6·82	0·320	0·123	0·626	0·304

N = Nitrogen.

She has a stepfather and her home life is very unhappy, but it is difficult to assess the importance of anxiety and mental stress as exciting her frequent attacks, since we know that the frequency and severity are as a rule greatest at her age.

(6) John Donnachie was the third child of Elizabeth W., who herself suffered from the disease. He was a normal full-time baby, and apart from the usual infections of infancy and childhood appeared to have enjoyed normal health until the age of 17 years, when he had a mild attack of paralysis in the lower limbs associated with the common prodromal feeling of stiffness during the night; the attack itself only lasted some three hours and he was then able to go about. He was working in a shipyard and in three subsequent attacks, all of a mild character, he never lost more than half a day's work, partly possibly because his attacks also were as a rule towards the end of the week,

when they were sometimes associated with dietetic indiscretions. He was also subject to periodic bilious headaches of a migrainous nature, but these occurred independently and never merged into a paralytic attack. His fifth and final attack occurred in July while all his family except his father were on holiday.

One evening, having done his usual day's work, he had a supper of fish and chips, and admitted to having eaten to excess of this dish, but retired to bed feeling quite well. At 3 a.m. he awoke and called to his father to come and turn him in bed as he was unable to move any of his limbs, and had in all probability been wakened by the malaise noted in these attacks from the inability to change the position of the limbs and body in bed.

The paralysis persisted throughout the day and he was able to eat and speak without difficulty, but he passed no urine and the bowels were confined. On the following morning he was unable to lift his head from the pillow or to raise himself in bed, and in addition he had a feeling as if there was some obstruction in his throat which interfered with his breathing, and frequently said, "I wish I could get this out of my throat and I would then feel better." He was still able to swallow however, and there was no impairment of his speech. He was able to eat his dinner during the day, but with difficulty, and at 2 p.m. he vomited some undigested food. At 3 p.m. his father gave him some whisky and hot water "as his breathing seemed bad": this appeared to make him choke and more vomiting ensued, resulting in considerable exhaustion. He then appeared to improve slightly and asked for a cigarette from a friend who had come in to look after him while his father went back to work; this was given to him, but as it had to be held in his mouth and his breathing was shallow it is presumed that he inhaled a quantity of smoke, and since the respiratory muscles were too weak to compete with the paroxysm of coughing which ensued, his breathing failed and death occurred.

III.—General Description of the Disease.

(1) *Ætiology.*—Theories as to the causation of this disease have been numerous. Dana suggested that it might be symptomatic of a recurring poliomyelitis, that is, of a chronic infection with exacerbations; but from what we know of the protective influence of an attack of that disease, such a theory appears improbable quite apart from the wide clinical and epidemiological differences. Those who are unacquainted with the condition almost invariably suggest a hysterical basis for the seizures and it is probable that some mild cases are missed on this assumption. Holtzapple, though he attributed the seizures to spasm of the anterior spinal artery, described migraine as occurring in ten out of seventeen patients who had periodic attacks of paralysis. Five of his patients had attacks of paralysis associated with headache, and thirteen other members of the family, who never suffered from paralytic seizures,

had periodic migrainous attacks. In some of his cases the headache preceded the paralytic attacks, making its appearance in early childhood and then ceasing when the paralytic phenomena developed, but in other cases the headache continued throughout, alternating with attacks of paralysis. This, however, is the only series so far recorded in which migraine appeared to be a factor of ætiological importance.

Holtzapple also, from his theory of the ætiology, ascribes the permanent paralysis, occasionally found in those who had suffered from recurring attacks for many years, to a slow degeneration of the anterior horn cells from frequent disturbance of their nutrition. He advances as an additional causative factor defective nitrogenous elimination based on urea excretion. The frequency with which muscular exertion and cold have been described as exciting factors naturally suggested that products of normal or abnormal muscle metabolism were instrumental in bringing about the paralysis, and it is to be noted in this connection that forms of spastic periodic paralysis have been described by Rich and also by Collier. In the former's own family five members suffered from transient recurring spastic paralysis of the face as a result of fatigue and exposure to cold, while the latter describes two members of one family in whom spastic paralysis of a severe type could be produced at will by withholding food and giving exercise. In a family of travelling merchants described by Collier the attacks seemed to depend entirely on the absence of food, and this was demonstrated by the fact that if they dined at 8 p.m. no attacks occurred, whereas if they dined early or missed their evening meal an attack occurred with certainty.

Auto-intoxication in association with constipation, menstrual periods, or dyspepsia, is also mentioned, as are lack of exercise, emotional excitement and fatigue. Neustadter found an exceedingly high blood calcium (20 mg. per 100 c.c.) in his case, and from this finding it has been suggested that the high blood calcium might explain the failure of the muscle to respond to electrical stimulation from the occurrence of some disarrangement of ions.

Buzzard put forward two theories as to the ætiology: firstly, that a chemical or physical change in the muscle plasma alone was not only a possible but the probable explanation of the loss of muscular contractility; secondly, that the important part played by the muscular system in the control of lymph circulation points to an unstable condition of the latter, or an abnormal or toxic condition of the fluid itself as possible sources of the changes in the muscles.

Some writers have stressed an analogy with myasthenia gravis, as

in some cases of that disease attacks of paralysis lasting a few days and resembling those of family periodic paralysis have been described by Collins and others. But though the rapid exhaustion of the muscular power and the failure of the muscle to respond to electricity are suggestive, yet attacks of family periodic paralysis as a rule commence after the patient has been asleep for several hours, and even though muscular exertion on the preceding day has been blamed by many patients for exciting an attack, such exertion, even far short of causing muscular exhaustion, is by no means a constant factor. Moreover, the electrical reactions are not similar, and lymphorrhages are not a characteristic finding in family periodic paralysis, where also the main incidence of the paralysis is not in muscles enervated from the brain-stem.

In Mitchell's case an attempt to determine the toxicity of the blood-serum gave inconclusive results, but we know from the work of Mouzon and Turpin that injections of the serum of epileptic patients into the circulation of animals produced convulsions which frequently had a fatal termination, whereas similar injection of serum from healthy people had no effect; further investigation of this nature is indicated in family periodic paralysis in view of the indefinite results so far obtained.

The transmission of the disease shows no characteristic features. In Holtzapple's series the disease was transmitted through a father who had attacks of paralysis in six instances; through the mother in four instances; through a father who had attacks of a migrainous nature in four instances, and through a mother who had migrainous attacks only in three instances. In nine instances the disease was transmitted through the father, and in eight through the mother. The members of this family who were thus affected were of varied occupations and intellectual attainments, and included a bricklayer, a seamstress, a school-teacher, a clergyman and a doctor.

The onset of the malady has been described as early as the second year and as late as the thirtieth, but it is most common for the first manifestations to appear about the years of puberty, and the severity is greatest between the years of 20 and 30, while it is during this period that the extremely rare instances of death occurring in an attack have been described.

More cases have been described in males than in females, but transmission may occur apparently equally through the members of either sex. Although the familial nature of the disease is now well established, isolated instances of the disease have been not infrequently reported.

(2) *Pathology.*—Autopsies have been exceedingly rare. In two of Holtzapple's cases in which post-mortem examinations were made, no pathological lesions were found to account for the disease. More recently Schmidt has reported two cases in which death took place at the height of an attack. In his first case the patient was said to have died of an intoxication from the alimentary tract, and hyperæmia was found in the nervous system as well as in other organs, but no specific lesions were discovered; unfortunately, the muscles do not appear to have been examined. The second patient, a brother of the first, died of cardiac failure in the course of a severe attack; here also there was hyperæmia of the organs and considerable cardiac dilatation, but nothing was observed in the central nervous system.

Biopsies of muscle have more frequently been performed. Oppenheim, Goodbody and Singer have described rarefaction and proliferative degeneration of the striated fibres with slight multiplication of their nuclei. They were not inclined, however, to attribute great importance to these findings, as they could not exclude the possibility of the changes being artefacts. Goldflam described a dissociation of primitive fibres with an increase in calibre and vacuolation, the sarcolemmal nuclei being also abnormally large. No interstitial inflammation, in fact no evidence of inflammation, and no nervous changes could be found. He compares these lesions with those found in progressive muscular atrophy. Schmidt noted similar lesions, and likewise compared them with progressive muscular atrophy and with the pathological findings in myotonia, but emphasized their resemblance to those found as the result of muscular ischæmia which he considered to be the basic cause of family periodic paralysis. He believed the paralysis in the latter condition is caused by a temporary arrest of the blood-supply to the muscles. All these results, however, are of little value, as the state of the muscles before, during and after an attack has not been studied, and it does not seem possible that gross alterations can occur at the moment of the attack. Further, we know that when the disease has been present for several years some permanent weakness in the muscles may develop, as noted in one of my patients.

Subsequent biopsies by other writers have given entirely negative results, so that the changes described above are now considered to be artefacts which have arisen in the course of preparation of the sections.

Holtzapple found a diminished excretion of urea in his cases, and noted also that the worse sufferers were those who showed the most marked diminution in the daily output of urea. His work was done,

however, at the beginning of this century, and there is no evidence that the patients were on a known intake of food or in nitrogen equilibrium before the amount of urea in the urine was estimated, so apart from there being no subsequent confirmation of the constancy of the decreased urea excretion in this disease, it is difficult to attribute much value to his findings.

Schlesinger, in an isolated case, found acetonuria in the majority of the attacks, and this was occasionally associated with albuminuria and the presence of hyaline casts, and Mitchell, Flexner and Edsall, from the examination on two occasions of the stomach contents of one of their cases, found that starch digestion was not proceeded with, and that there was total inacidity. Goldflam and Croft found the urine hypertoxic to laboratory animals.

The relation of creatinine excretion to disease of muscular tissue has been investigated by many writers and most chemical-physiologists appear to believe that the excretion of creatinine in the urine bears a direct relationship to the amount of muscular activity, but in cases of family periodic paralysis the findings have been inconsistent. Taylor found that the creatinine output was diminished both before and during an attack. This was confirmed by Mitchell and Flexner, who also noted an associated diminution in the excretion of ammonia, and with the onset of recovery a return of the creatinine excretion to a normal figure.

Spriggs noted that creatinine is excreted in smaller quantities than normal when the bulk of the muscular tissue is diminished, as in the primary myopathies, and also when muscular activity and muscle tone are depressed by a pathological condition of the muscles or motor apparatus, as in myasthenia gravis and amyotonia congenita, but that the output is unaffected by loss of muscular tone through interference with the sensory path, as in locomotor ataxia. He considered, therefore, that creatinine was connected not only with the bulk of muscle but also with the normal development of muscular function, and while admitting that by far the greater part, if not all, of the endogenous creatinine in the urine is derived from muscular tissue, he held that creatinine is a product of the internal metabolism of muscle and not of its contraction.

The chemistry of creatin and creatinine has also been thoroughly investigated by Hunter, and the low output of creatinine in muscular dystrophies has been confirmed by many writers, notably by Burger and Meyer, and also by Gibson, Martin and Buell. Similar results

have been described in amyotonia congenita by Gettings and Pemberton, as also by Powis and Roper, and Pemberton has also found a low creatinine output in myasthenia gravis.

In family periodic paralysis we know that it is customary for the paralysis to make its appearance after a night's rest, but Cuthbertson, on investigating the influence of prolonged rest on muscle metabolism, found that in subjects who were in a condition of nitrogenous equilibrium, and who thereafter spent periods from five to thirty-two days in bed, there took place a rise in urinary nitrogen due to a proportionate increase in the amount of urea. The excretion of creatinine and uric acid, however, was practically unaltered.

In addition to the muscular dystrophies, the excretion of creatinine is largely reduced in extensive paralysis as well as in other conditions in which the activity of the muscles or their bulk is largely reduced, while during the process of wasting of muscles, as in the cachexias and after severe exercise, the amount increases.

In three cases of family periodic paralysis, Mitchell, Flexner and Edsall noted a marked diminution (3 to 80 mg.) in the creatinine output of the urine, along with a diminished excretion of ammonia preceding and during the paralytic attacks, with a sudden rise to normal (880 mg.) following recovery. From these findings it is thought that the attacks are due to a metabolic disturbance which is situated chiefly or entirely in the muscles themselves rather than that the attacks are due to retention of creatinine.

In my series it was only possible to have one patient on a fixed diet for a period between the attacks sufficiently long to get establishment of nitrogenous equilibrium and the urinary findings while in apparently normal health, and in this patient during subsequent attacks a definite increase in the excretion of creatinine in the urine was found.

(3) *Symptoms.*—The onset of the attacks has been described as occurring as early as the fifth year and as late as the thirtieth, but it is most common for the first manifestations to make their appearance about puberty. There is a tendency to a diminution in the frequency and intensity of the attacks after middle life, similar to what is common in migraine, and one of my patients was free from attacks for fifteen years before his death at the age of 70.

As in migraine, patients often say that on the day preceding an attack they have felt exceptionally well, and have not only accomplished an active day's work, but have taken exercise in addition. Similarly, bulimia is frequently present, and relatives have found it noteworthy

the amount of food required to satisfy the patient's appetite on these days. Moreover, not only is the appetite sharp, but there is often a craving for rich and heavy food, or even for specific articles of food, such as fruit or meat. The prodromata may be constant or variable in different patients, but they are usually the same for one individual, and sometimes for all those affected in one family. All the usual prodromata can occur without a typical paralytic attack ensuing, but most commonly they foretell an attack.

The majority of those affected waken in the early hours of the morning with a feeling of malaise, stiffness and weakness in the limbs, or they may even waken with the paralysis fully developed, when in such a case discomfort from inability to change the position of their limbs in bed appears to be the factor which arouses them from sleep. As a rule those patients who waken with the feeling of stiffness and weakness in the limbs are able to go to sleep again to waken at their usual hour with the limbs paralysed.

There is considerable variation in the *marche* of the paralysis. Thus a patient may waken completely paralysed, having had no warning of an attack, or having wakened at night with such prodromata as mentioned above; he may again waken at his usual hour with some slight paresis of the limbs only, and some hours may then elapse before the paralysis is complete.

More rarely attacks begin during the day and, in my experience, such are slow in onset or even of an abortive type, but Osler describes unconsciousness and also inco-ordination of the limbs as ushering in a diurnal attack.

By day more often there is a feeling of malaise, general fatigue and weakness which forces those affected to lie down, and as foreshadowing attacks by day, affections of character, irritability, emotionalism or erotic manifestations are sometimes present. It is to be noted that in women attacks are not infrequently associated with the menstrual periods.

Many of the attacks which occur by day are of an abortive type; one patient in my series had numerous such attacks. They may vary from merely a stiffness and weakness in the lower limbs to a slight paresis with weakened response of the tendon reflexes and slowing of muscular contraction. These abortive forms are usually dispelled by lying down for one or two hours with the application of additional clothing or heat.

In the fully developed attack the patient lies in bed with powerless

but not atonic limbs, unable to raise the head or to change his position in bed, and the latter disability in a long attack is to the patient about the most unpleasant feature. In the majority of cases the cranial nerves are not seriously affected, but it is not uncommon to find that there is some embarrassment of their function, so that coughing or sneezing may be impossible. Speech is more rarely affected and this is probably often due to paralysis of the expiratory muscles. Two patients in my series frequently suffered from such bulbar affections and both died as a result of this involvement. Paralysis of the palate has been described by Janota and Weber.

The paralysis is the primary feature and has the appearance of a peripheral or lower motor neurone lesion in that it is not of a spastic type and the deep reflexes are absent or sluggish.

Occasionally after having reached its maximum intensity, as a rule several hours after its commencement, the paralysis is diminished slightly and is then intensified before disappearing. The voluntary muscles are mainly affected, especially the muscles of the limbs; in the majority of cases the muscles of the lower limbs are first and most severely affected, and sometimes a paraplegia may be the whole manifestation of an attack. More rarely the upper limbs may be alone affected and even a hemiplegic distribution, or a monoplegia, may occur. In the most common form of attack, however, there is usually perfect symmetry in the involvement of muscles.

The muscles of the abdomen are usually affected in the ordinary form of attack, but on the whole the flexor muscles are less affected than the extensors, while in the more severe attacks the intercostals and accessory muscles of respiration are involved.

Although it is uncommon for urine to be passed during an attack lasting twelve to twenty-four hours, yet when the paralysis persists for two or three days urine is voided normally as the bladder becomes distended. A temporary anuria associated with profuse sweating has been observed, and Clarke describes cases in which micturition was difficult or impossible, as well as a case in which incontinence occurred; his experience, however, is very unusual. Erection, although usually absent during an attack, has, however, been described.

Though various paræsthesiæ occur as prodromata, the integrity of all forms of sensation is a feature of an attack. It is true that there is occasionally complaint of pain in the paralysed limbs during a seizure, but this probably results from the inability to move leading to the prolonged maintenance of the limbs in one posture, aggravated perhaps by the associated hypothermia and sweating.

Consciousness is absolutely unimpaired throughout the paralytic state and in the two patients in my series in whom death took place at the height of an attack consciousness was preserved till the end.

The occurrence of death during an attack is extremely rare; Holtzapple was able to collect six instances, including one personal case, the determining causes being paralysis of the respiratory muscles, cardiac dilatation and failure, or an inhalation bronchopneumonia.

The duration of the paralytic attacks varies from hours to days, but in general the duration of the attack is in direct proportion to its severity. The muscles first paralysed are usually the first to recover the power of movement. In general, once recovery commences the *restitutio ad integram* is rapid, but after recovery there is usually a feeling of fatigue, lassitude, or slight headache with a diminution in the activity of the tendon reflexes, and some writers have described several loose stools or even actual diarrhœa as occurring at this stage. Hyper-excitability of the facial nerve (Chvostek's test) has been found by Janota and Weber at the end of an attack.

It is claimed that certain of the paralytic attacks can be shortened by massage, induced sweating, purgation or by passive movements, but I have been unable to confirm this in my series, though certain of my patients have been able, like others recorded, to "walk off" threatened attacks by rising from bed when prodromata occurred and walking about for variable periods.

In addition to the paralysis there are also certain associated neurological phenomena, of which the most important is the disturbance in the electrical reactions of the affected muscles. Goldflam noted hypo-excitability of the affected muscles to the galvanic and faradic currents during an attack and even a partial reaction of degeneration. His findings as regards polar changes have not been confirmed by all those who subsequently reported cases of this disease, but in the majority of instances there has been a diminution or failure of response to the faradic current, and in many absence of response to galvanic stimulation also. In muscles partially paralysed the loss of electrical excitability is proportional to the degree of paralysis. Collier, however, while agreeing that in the paralytic attacks there is loss or diminution in the response to the faradic current, has found no change in the galvanic response.

In my patients in whom the electrical reactions were tested during a severe attack, no response was found to faradism or galvanism during the period of complete paralysis, while in the transient, brief, or abortive attacks slight or no diminution to the faradic current was found. In

the case of some standing already mentioned, where the leg muscles showed the consistence found in certain myopathies, there was a diminution in the response to the faradic current compared with that found in the rest of the body in the quiescent period between attacks

The tendon reflexes are absent during an attack, and as previously mentioned it may be some time after an attack before normal responses are obtained. In those who are severely affected by the disease as evidenced by the frequency of the attacks, there may occur a permanent loss of tendon reflexes; this was well-marked in my patient, J. W., whose attacks were very frequent over a period of years and whose father had also suffered from the disease and died in a paralytic attack. The knee-jerks are most commonly lost, but in the above instance the ankle-jerks were also absent and the arm-jerks on both sides were extremely sluggish. The disappearance of postural and pharyngeal reflexes in the later stages has also been described. Between attacks the patient's condition otherwise is absolutely negative both from a subjective and objective point of view, but very slight and abortive attacks are not uncommon, perhaps affecting only some groups of muscles in the lower limbs and necessitating only a brief rest before the patient is able to go about again.

Profuse sweating is common and as a rule is greatest at the full development of an attack, though rarely it has been described as reaching its maximum while recovery is commencing. Sleep is normal, even during attacks which last for some days, except for that discomfort due to inability to change the position; somnolence has been rarely noted as a prodromal symptom, and Fischl declares that sleep sometimes occurs as the equivalent of an attack.

In three cases described by Buzzard, a mother and two sons, the onset of the attacks so definitely occurred during a period of rest following active exercise that he was easily able to have attacks induced for his observation. In the case of the mother the onset was so fulminating that in the course of a few minutes she was unable to rise from a sitting or lying position; she had also a choking sensation during an attack and sometimes more definite respiratory embarrassment; in addition mastication and speech were only carried out with a certain amount of fatigue.

The sons were emotional and easily upset during attacks, and in one alarming signs of syncope occurred during the seizures. They were sometimes affected two or three times a day, but less severely than their mother; and recovery occasionally took place in half an hour

even when the muscles of all the limbs had been paralysed, with inability to sit up, slight bilateral ptosis, dysarthria, and absence of electrical response in the affected muscles. In one attack in which the patient following active exercise became unable to raise himself from a chair or his arm above his head, he was able, after only a period of ten minutes, to walk again, although with difficulty.

In addition to the diminution in the reflex response it is not uncommon to find in those patients who have suffered from recurring paralytic attacks for many years some permanent change in the muscles with or without persisting paresis. The muscles may have that fibrous or rubber-like consistency which one finds in certain of the muscular dystrophies, and even changes of a pseudo-hypertrophic nature have been recorded. Moreovor cases of family periodic paralysis have been described in which other members of the family who had never suffered from periodic or any paralytic attacks presented the clinical picture of one of the muscular dystrophies. The association of family periodic paralysis with myasthenia gravis I have already described. Whether such changes indicate a co-existing muscular dystrophy, or a specific dystrophy associated with the muscular involvement in family periodic paralysis, we do not as yet know. In cases thus associated with dystrophy of muscles Janota and Weber found in the intervals between paralytic attacks a qualitative modification in the electrical excitability tending towards a myasthenic reaction, and in other cases reactions resembling those found in veratrinized muscle and in Thomsen's disease.

Atwood has noted a transitory albuminuria, and Schlesinger acetonuria during attacks. Several other writers having found indicanuria have stressed its presence as evidence of abnormal destruction of protein in the lower bowel and have blamed constipation as an exciting factor.

Dilatation of the heart has been described by Holtzapple, Oppenheim, and by Janota and Weber in an attack along with weakness of the pulse, and slowing and arrythmia of the latter have also been observed. Systolic murmurs have been noted in association with the dilatation, and the dilatation has been confirmed radiographically by Fuchs. Electrocardiographic tracings were taken by Janota and Weber both during and between the attacks. In one of their patients, when the vascular complex was normal between the attacks with a definitely positive T, they found accentuation but not enlargement of R in leads 1 and 2, with T diphasic and poorly defined. These findings are not in

favour of unilateral preponderance or of any affection of the conduction of ventricular action, but they do resemble the changes found by Rothberger in a patient showing a marked degree of vagotonia Arterial hypertension has also been described.

Some affection of the digestive system is not uncommon during an attack. Diminution of appetite is usual, and eventually complete anorexia occurs, but sometimes, as in the prodromata, there is a craving for special articles of food, such as fruit and meat. Goldflam has described nausea and vomiting as accompaniments of attacks, but these are uncommon phenomena. From the diminution of muscle tone and of intestinal peristalsis constipation and flatulence are freqnent. Enlargement of the liver with great thirst has been noted as well as the secretion of extremely thick saliva, but of all the digestive symptoms described anorexia and thirst are probably those most commonly found. Although the bowels are usually confined, in two of my patients in whom the attacks lasted four and two days respectively the bowels moved normally on their being carried to stool.

The blood picture was found by Wexburg to resemble that found in Graves' disease, while Goldflam noted a neutrophilia with eosinophilia, and Taylor a basophilia even reaching up to 51 to 57 per cent. As a rule, however, examination of the blood has shown no definite abnormality, and though a moderate lymphocytosis has been noted by some writers, we have no information as regards the time, in relation to meals, at which their examinations were made. The blood-sugar has been found by Janota and Weber to be a little above the normal figure, and the same authors along with Neustaedter note an increase in the height and duration of the blood-sugar curve after the ingestion of glucose, but without the occurrence of glycosuria. The diminution in the amount of the serum-calcium described is of interest in association with the cramp-like pains noted by some patients as prodromata, and with the occurrence of the Chvostek phenomena.

(4) *Diagnosis.*—A complete neurological examination during an attack should exclude hysteria, and investigation regarding familial nervous disease should in the majority of cases make clear the diagnosis.

The complete preservation of consciousness distinguishes family periodic paralysis from epileptic attacks, even from the rare paralytic type described by Higier.

Landry's paralysis, the transitory paralysis of myotonia, myasthenia gravis, and the paralysing form of vertigo described by Gerlier, need

only be mentioned in the consideration of differential diagnosis as in all of these there are other characteristic symptoms and signs.

Some writers have described the occurrence of the muscular dystrophies in the families of patients suffering from periodic paralysis, even the pseudohypertrophic form having been described. Thomsen's disease, or at least the presence of electrical reactions of a myotonic type, has been noted, while progressive muscular atrophy has also been recorded in association with the disease.

Only rarely have epileptiform seizures been described in addition to the attacks of paralysis, but there has been an association of family periodic paralysis with Higier's épilepsie paralytique. Migraine, urticaria and other conditions where an anaphylactic basis is thought probable, have also been described as associations, as have also certain psychical affections, and while tetany itself has not actually been found as an accompaniment of the paralytic state, yet the electrical reactions similar to those found in tetany, and a Chvostek's sign, have been noted.

Discussion.

I attribute great importance to the association of migraine with paralytic attacks in the series of cases of family periodic paralysis recorded by Holtzapple, the largest series yet on record. Holtzapple observed in four generations of one family 17 cases of periodic paralysis. In this family also, 18 members suffered from periodic sick headaches of a definitely migrainous nature ; 5 members suffered from such headaches associated with paralytic attacks, 14 had attacks of headache only, and 13 had attacks of paralysis only. The total number affected with either paralysis or headache was 32. Holtzapple believed the headache to be an equivalent of a paralytic attack. Although this association has not been noted by those who have since described cases of this disease, it has been present in two cases in my own series.

In migraine the influence of a deficient digestive function appears to be of importance. The affection of the digestive function by physical processes is generally admitted, and Cannon has shown experimentally that emotion plays an important role in the movement of the stomach, by demonstrating that peristalsis ceases whenever the animal shows signs of rage, distress, or even anxiety. Since mechanical stretching is the stimulus which produces contraction of plain muscle, such as that in the stomach and intestines, it follows that when the muscle is atonic, as is commonly the case in migraine, there is passive or flaccid distension

with abeyance of peristalsis, so that stasis and decomposition ensue, and the possibility of decomposition is further enhanced by the deficiency or absence of secretion of free hydrochloric acid in the stomach, a function also much influenced by psychic processes.

Alvarez has described cases in which fright or shock has caused for hours inhibition of the digestive processes in the stomach, while mental exhaustion, anxiety states and physical exhaustion, are similarly associated with cessation or impairment of gastric digestion.

In two of my cases of family periodic paralysis in whom fractional test meals were performed, disturbance of gastric function was evident; in one, achylia gastrica and deficient starch digestion were noted, and in the other, even at the end of two hours, digestion of starch had not taken place. In six cases of migraine thus investigated, I have found similar changes, and radiological examination showed atony, and on some occasions delay in the advance of the barium. Indicanuria, although not constant in these conditions, is occasionally found, and this suggests that intestinal decomposition is taking place as a result of the digestive deficiencies. As a result of deficient gastric digestion, abnormal metabolic products thus formed may not only produce the symptoms of a general toxæmia, but by their action either directly on the sympathetic system or by stimulation of the vasomotor nerves in the vessels, may cause changes in the central nervous system common to both diseases. Moreover, the possibility of absorption by the vagus of toxins from the stomach itself has also been described. Loeper, Forrestier and Tounet found in the trunk of the vagus tetanus virus and formol which has been administered by the stomach, and these they believed to have reached the nerve through minimal lesions in the gastric mucosa. These authors have also noted the presence of an increase in chlorides in the vagus during digestion, and moreover have found pepsin in the cerebrospinal fluid, while tetanus toxin administered by the stomach has later been identified in the medulla, but not in the brain itself.

In the further consideration of the relationship between family periodic paralysis and migraine, we know that in migraine paralysis may occur, not only of the ocular muscles, but sometimes of an arm, and even more rarely of a hemiplegic distribution. Bulimia is a common precursor in both conditions, and although sufferers from migraine usually go to bed on the day preceding an attack with no warning that it is impending, yet, as in family periodic paralysis, it is most common for them to waken with the headache and feeling of

lethargy and intoxication in the morning. While in family periodic paralysis the attack is said to supervene during sleep or in a state of rest following a period of muscular activity, in migraine worry and mental exhaustion are more common as exciting factors than physical exhaustion.

Our ignorance of the pathology of epilepsy makes it of little value to contrast the attacks of idiopathic epilepsy with those of familial periodic paralysis, but it is interesting to consider certain factors common to both conditions. These are the influence of heredity, the cyclical nature of the attacks, which are associated in some patients with dyspepsia and evidence of intoxication, while in others they are associated with endocrine dysfunction, and, if infrequent, may only occur in association with menstruation. In general their occurrence can often be related to some metabolic disturbance associated with an affection of the vegetative nervous system. Moreover, a certain number of those who suffer from migraine in childhood or adolescence subsequently develop epilepsy, while a history of migraine and of other neuropathic conditions among the relatives of epileptics is not uncommon.

In spite of wide difference in the manner of onset and duration of the attacks, yet narcolepsy, the pathology of which is also still unknown, calls for consideration in respect of the analogies presented by the cataplectic seizures. The attacks of cataplexy, incited usually by an emotional state, and of a duration measured in seconds, are of an atonic flaccid nature, and in the attack personally observed by Kinnier Wilson reflex activity was lost and a unilateral extensor plantar response was present until two minutes after the recovery of power, while a temporary disturbance in the electrical reactions has also been described. Although these fulminating palsies present a picture similar to that developed, after hours or days, in periodic paralysis, yet there is no familial neurological taint and no evidence of intoxication, and while agreeing with Adie that narcolepsy and cataplexy are probably both of the nature of inhibitory phenomena, I do not consider that this theory is applicable to familial periodic paralysis.

It is difficult to believe, however, that in family periodic paralysis the presence of some toxin in the blood could alone account for the attacks of paralysis, which are the main features of the malady and which may last for some days, especially as we know that during the whole of the attack it is usual for the excretory functions to be inactive, so that the elimination of such a circulating poison is unlikely. Moreover, in intoxications affecting the lower motor neurones the peripheral

muscles are first affected, and volitional movements are diminished or lost for a considerable time before the electrical reactions are impaired, whereas in family periodic paralysis the response of the muscles to voluntary and electrical stimulation disappears *pari passu*, and following even complete paralysis the recovery to volitional and electrical stimuli is equally quick. Those facts, as well as our knowledge that muscular exertion or exhaustion is not a constant predisposing factor in all those who suffer from the disease, enable us to oppose those theories which have been advanced that normal products of muscular activity either in excessive strength, or acting in the presence of lowered body resistance, can cause the paralysis of the muscles in this disease. The suggestion that a poison with a seat of selection in muscular tissue similar to curare is the cause of the paralysis is opposed by our knowledge that the muscles of curarized animals show no electrical changes. It appears therefore improbable that this disease is caused by a general intoxication *per se*, and we must therefore consider the possibility of some abnormality in the muscle tissue itself, which may be unduly sensitive either to a general intoxication or to the local metabolic changes which result from prolonged or extensive muscular activity.

We know that relatives of those who are affected with family periodic paralysis have been found to suffer from various forms of the muscular dystrophies, and we know also that those who have suffered from the periodic paralytic attacks for some years may themselves exhibit weakness and the physical changes characteristic of the dystrophies, so that it is not improbable that some abnormality of the muscular tissue is a feature in those who suffer from family periodic paralysis.

When we consider that in some patients the attacks of paralysis have definitely followed severe exercise, or have taken place during muscular repose, as during sleep, following upon the general fatigue of a hard day's work, we are led to wonder whether there may not be some interference with the circulation of the blood or lymph preventing the removal of the products of muscular metabolism.

As regards the circulation of the blood, it may be noted that in some cases, and especially in those I have personally described, cold has been a definite exciting factor, and may to some extent have been responsible for an inadequate circulation in the extremities which are the most frequently affected parts of the body, and may thus have interfered with the removal of the results of muscular activity, and as I already postulated a stimulation of the vasomotor system by toxins of

a gastro-intestinal origin, interference with the circulation may also take place from this cause.

The lymphatic circulation is, however, much more dependent on muscular contraction, and since the attacks most commonly commence during a period of rest or sleep following muscular activity, it is possible that the accumulation in muscle of products of its metabolism may be sufficient to cause changes in its substance which can affect its function of contractility. Moreover, during sleep respiration is more shallow and the blood-pressure is lower, so that the circulation of blood and lymph is further depressed.

Certain points noted in the disease appear to support such theories. Firstly, some patients on becoming aware of the onset of an attack are able, as they themselves say, "to walk it off" by getting up while the limbs are still only stiff and slightly paresed, moving them forcibly and then walking about, though it is to be noted that such attempts more often delay the development of a complete attack than actually abort it. The above theories may also account for the escape of the diaphragm, as the incessant activity of this muscle in voluntary respiration, and even during sleep, would prevent any stagnation of lymph in its substance; similarly the fact that the muscles supplied by the cranial nerves are infrequently and incompletely paralysed may be due partly to the fact that these muscles are in a state of some activity even when the muscles of the body in general are at rest, and the position of those muscles, above the junction of the lymphatic and venous systems, allows the effect of gravity, even while in bed, to aid their lymph return.

The fact that the muscles in an attack are not hypotonic but have a firm feeling, without there being any suggestion of spasticity, supports to a certain extent the view that the excessive lymph formed as a result of muscular activity remains and perhaps forms abnormal combinations in the muscle tissue, thus causing the firm consistence or induration in attacks, and also the permanent changes found in the muscles of those who have suffered from many attacks over a period of years. The fact that the muscles, in what is apparently a flaccid palsy, show no decrease or alteration in tone is of interest, and it is to be noted that in hypotonia found in other clinical states no definite alteration in the electrical reactions of the hypotonic muscles is to be found.

Although interference with the circulation of both blood and lymph may be present, and although it is possible that such changes could interfere with the muscle function of contractility and maintain a state of paresis, yet I feel that the paralysis is fundamentally due to the

presence of a constitutional defect in the muscle; and we can, I think, obtain confirmation of such a possibility from the consideration of certain hereditary tissue defects.

For the purpose of my thesis I would draw attention to one of the dystrophies, namely dystrophia myotonica, in which there is an indication that the neuro-muscular defect may be only part of a general constitutional abnormality. The condition is familial and usually first manifests itself about the age of twenty, but while it may be directly transmitted as a rule through males, yet more frequently a latent tendency may be traced through various relatives by evidence of bodily dyscrasias which are a feature of the disease. Of these cataract is most common, but changes in the thyroid gland, premature baldness, and testicular atrophy are also frequent, although it is to be noted that sexual life is usually normal until the onset of the disease. Other occasional findings are a relative lymphocytosis, increased irritability of the facial nerve, and most constantly vasomotor disturbances, especially cyanosis and coldness of the extremities.

In family periodic paralysis, in which there is the development of a characteristic syndrome in member after member of a family at about the same period of life, we find something in common with dystropia myotonica, and although there are specific outstanding features in both conditions, yet it is evident that the basis in both is an abnormal constitution or diathesis.

From a comparison of family periodic paralysis, with migraine and epilepsy, I have indicated that instability of temperament and a liability to periodic intoxications are features common to the three conditions, yet, while in familial periodic paralysis the muscular defect is not of the nature of a true abiotrophy, in that the condition is not always progressive and may even in the latter years pass away, I nevertheless consider that there is some inherent muscular deficiency upon which a periodic disturbance of the vegetative system, with associated intoxication, acts to produce the paralytic attacks.

Summary.

Six cases of familial periodic paralysis are described in three generations of one family, and the histories of families previously recorded as suffering from this disease are reviewed.

The condition tended to develop about the age of 17 or 18 years in each member of the family, and in some patients who have suffered from paralytic attacks for years there was a development of permanent

muscular weakness and rarely the picture of one of the muscular dystrophies; the occurrence of muscular dystrophies in other members of the families, who were not themselves affected by periodic paralysis attacks, is also described.

The condition is compared with migraine, epilepsy, and certain heredo-familial degenerative diseases.

It is considered that two factors are concerned in causing the attacks of paralysis.

(1) An abnormal constitution of diathesis in which there exists, in patients with a neuropathic inheritance, a condition of disequilibrium of the vegetative nervous system with evidence of periodic intoxication associated with abeyance of the digestive function and abnormal metabolism at the time of the attacks.

(2) Some abnormality in the muscles themselves.

It is believed that the attacks of paralysis are caused by the low resistance of the defective muscle to abnormal metabolic products present during the periods of intoxication, while it is probable that interference with the blood and lymph circulation in the muscles, which results from the disturbance of the vegetative system, is a contributory factor.

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ATROPHY AND DEGENERATION IN THE MUSCLE SPINDLE.[1]

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THE spindles of skeletal muscle are structures receiving both dorsal-root and ventral-root innervation. They have, therefore, presumably both sensory and motor function. Hence, for study of the trophic dependence of tissue on innervation, the spindles afford a unique object.

Incomplete and conflicting evidence still obscures the condition of the spindle in the atrophy and degeneration of muscle consequent on denervation. In his pioneer work on the anatomical constitution of the nerves of muscle, Sherrington reported (1894) that the spindles remained intact when the bulk of a muscle was altered almost beyond recognition. His animals, cats, survived sciatic section five months. Horsley confirmed Sherrington in 1897; but in the same year Batten published his much more extensive studies. He examined the spindles in various pathological states of man and following peripheral nerve lesions in cats. In the latter he found the spindle muscle fibres atrophied in proportion to the time elapsing after operation. Later, Boeke (1916) again reported such degenerative changes, the result of peripheral nerve lesion. However, the only data on the trophic relations of the nerve roots to the spindle were presented by Onanoff, in 1890, thus antedating Sherrington's experiments. On the slighest of evidence, Onanoff concluded that the spindle was in trophic and motor dependence on the anterior horn cells.

Thus the problem of the trophic relationship of the muscle spindle to the nervous system opens itself to attack in two stages. First, the reaction of the spindle to peripheral nerve lesion must be definitely established. Then, if the spindle shows atrophic and degenerative changes, the responsibility of the various components of peripheral

[1] This study was commenced while the author was a Fellow of the Henry Strong Denison Medical Foundation.

innervation, the dorsal and ventral root components, and possibly the sympathetic, for maintaining the normal state of this complex sensori-motor organ, must be analysed.

I.—The Reaction of the Muscle Spindle to Peripheral Nerve Lesion.

Material and methods.—Peripheral nerve lesions were produced in six young adult cats. The brachial plexus was exposed, under ether anæsthesia, from the axilla to the elbow. The component nerves (radial, median, ulnar, musculo-cutaneous, medial external cutaneous) were isolated. One to three centimetres of each nerve was excised, and the cut ends turned back and tied to the trunk. In order to eliminate sympathetic nerve fibres which might travel to the periphery along the blood-vessels, the stellate ganglion was removed in one of the animals (S VIa). From two more (S VIc, S VId) this ganglion and the entire cervical sympathetic chain were removed. The stellate ganglion was reached through the vertebral end of the first intercostal space by entry below the scapula. The cervical sympathetic cord and ganglia were exposed by an incision the length of the neck.

Pairs of animals, one with simple brachial plexus section and the other with the added sympathetic denervation, were allowed to survive four, six and twelve months. Because of these long survival times, the possibility of regeneration had to be considered. For the sympathetic lesions, this was not a problem; the post-ganglionic cell bodies were gone. Furthermore, the persistence of vasomotor and sudomotor paralysis was evidence that sympathetic nerve fibres were not present. The somatic nerve fibres gave signs of regenerating only in the two animals surviving operation a year. In one of these (S VId), at the time of death the reaction to pin-prick had returned in a strip extending down the anterior border of the forearm, but not on to the wrist. In the second (S IIe), so rapid was the return of sensibility that in the twelfth, and again in thirty-sixth week, the brachial plexus had to be re-exposed, the proximal stumps of the nerves located and an additional length of each removed. There was at no time, however, in any animal a recovery of lost motor function. Subsequent examination of the histological preparations confirmed the completeness of the denervation for all the cats except one. In this animal (S IIb), killed four months after operation, a small number of nerve fibres in an early stage of regeneration were found distributed through the interosseous muscles. About one-half of the spindle capsules contained nerve fibres, though

no definitive equatorial or polar endings were formed, and a smaller proportion of the old motor plaques of the extrafusal muscle fibres also received nerve fibres.

When the time of survival allotted a cat had expired, the animal was killed with ether, the aorta cannulated, and two litres of physiological salt solution perfused through the blood-vessels. This was followed by one or two litres of the fixative, 20 per cent. neutral formalin. After the material had stood in the fixative six months or more, specimens for histological study were removed and put through a modified Bielschowsky silver technique. The entire fifth interosseous muscle and the lateral slip of the fourth were cut serially, longitudinally at 15 μ. Cross-sections were made at 10 μ, from the middle of the belly of the remaining three slips of the fourth interosseous muscle Specimens from the side of operation and from the normal side were treated alike in each case.

Control.—The two muscles, the fifth and fourth interossei, were selected for concentrated study, because it was thought that in this way a standard might be established both for the number of spindles present in the muscle and for their form. Thus, ten normal fifth interosseous muscles yielded an average of nineteen spindles each, with a maximum of twenty-four and a minimum of fourteen. For the lateral slip of the fourth interosseous muscle, the average was five spindles; the range, two to nine. Curiously enough, there seemed to be little correspondence between the number of spindles in the same muscle from opposite sides. For example, in one animal (S IIf), the left fifth interosseous muscle contained twenty-two spindles; the right, fourteen.

A variety of spindles were found in the cat's interosseous muscles. There were simple spindles, and compound; spindles with a short equatorial region, and those in which this structure took in the greater portion of the spindle. There were spindles with small tight capsules, and with voluminous capsules; spindles with two intrafusal fibres at a maximum, and spindles with twelve. But all these are quantitative variations on one spindle pattern which has been repeatedly described by a series of investigators before and since Sherrington (1894). Plate III shows the typical appearance of the normal spindle in longitudinal and cross-section.

The manner of innervation of these muscle spindles has also been well expounded, most recently by Hinsey (1927) and by Hines and Tower (1928). To the conclusions arrived at in these papers the present study has nothing to add, except a conviction that the rich

confusion of nerve fibres at the spindle poles and in the capsule has not yet been thoroughly analysed.

Observations. — Following peripheral nerve lesions, the muscle spindles atrophy and degenerate. Moreover, the reaction of the intrafusal muscle fibres is quite in proportion to the reaction of the extrafusal, and of the same nature. For both, the duration of the lesion is the chief factor. Thus, after four months' denervation atrophy was far advanced. This was attested grossly by the diminished bulk of the muscle. Microscopically, the signs of atrophy were also largely quantitative. The muscle fibres were thinner and shorter; the brilliance of striation subdued. But at four months evidences of actual degeneration were scanty. Even after six months the picture was still predominantly one of atrophy, although large areas of degenerating muscle were now to be found. Throughout this material there was no difficulty in finding the spindles. They did not, it is true, stand out in the manner described by Sherrington and by Horsley. Indeed, connective tissue had so bound the capsule to neighbouring structures on the outside, and to the axial bundle within, that the spindles were much less conspicuous than normal, the more so since the striking nerve fibres and endings were also wanting. However, a complement of spindles well above the lower limit set by the control material was always found. Furthermore, in cross-sections there was no difficulty in making out a number of intrafusal muscle fibres also up to the normal.

After a year of denervation, however, degeneration was far advanced. Well-preserved extrafusal muscle fibres were to be found only here and there in the mass of fibrous tissue. And although a sufficient number of spindles were located in the interosseous muscle from the side of lesion (S IIe, 18; S VId, 22), this was only by vigilant search. Within the individual spindle, recognized perhaps by a fragment of the equatorial nuclear aggregation within a thickened capsule (fig. 4*a*), degeneration had frequently gone so far that no estimate of the number of intrafusal fibres could be arrived at. And the polar regions of these spindles (fig. 4*b*) had become indistinguishable from the surrounding fibrous tissue. Curtailed thus in length, enclosed in a narrowed and thickened capsule, the spindles were, indeed, almost lost in the fibrosing mass that had been muscle.

The two processes—atrophy and degeneration—are consecutive, and more clearly distinguished by dictionary definition than in fact. For the extrafusal muscle fibre, the stages of degradation may be briefly out-

lined. The nuclei reacted first. They became large and oval, and more deeply embedded in the fibre. Instead of the multiple small nucleoli characteristic of sarcolemma nuclei, there was a single large nucleolus, or none. The cross-striation faded, the light band becoming wider and the dark band paler. Fracturing along the line of cross-striation was common. At the same time the longitudinal disposition of the myofibrillæ became emphasized, especially toward the ends of the fibres, and along these lines the fibres also split. And preceding and accompanying these changes there was the progressive reduction in the size of the fibre which is the chief feature of atrophy.

Final destruction of the muscle tissue followed either of two courses. There was an acute process of degeneration, more conspicuous in the first half-year after the lesion than later. The entire length of a fibre, losing all semblance of internal structure, was reduced to a vesicular or vacuolated mass in which the swollen nuclei were quite irregularly disposed. The sarcolemna lost its sharp straight outlines and the contents of the fibre collected in lumps. At many points the sarcolemna seemed to break. This process, especially when it affected a group of muscle fibres, was attended by the infiltration of numbers of round cells, chiefly of a mononuclear type. At a later period, six months or a year after denervation, this acute process of degeneration was reinforced by a second degenerative process. Beginning toward the ends of a muscle fibre, the cross-striation disappeared and the myofibrillæ stood out as discrete strands. The nuclei, caught now between the fibrils, became extraordinarily elongated and the sarcolemma less clearly delimited fibre from fibre. Indeed, a year after denervation, it was usually impossible to discriminate the individual fibres of a fascicle cut in cross-section. Gradually, by these changes, the muscular tissue was reduced to a fibrous state. The muscle fibre became, to all appearance, a tendon filament, and the whole muscle a broad, flat tendinous mass.

All the features of atrophy and both processes of degeneration just described for the extrafusal fibre were exhibited by the intrafusal fibres as well (Plate IV). In the polar regions, especially, the reactions were identical. The muscle fibres first became thinner and shorter. Their nuclei, already central and oval, swelled. The cross-striation regressed and the myofibrillæ stood out prominently. Some fibres showed vesicular degeneration, but the majority were involved in the fibrotic process. Fig. 3*b* illustrates both degenerative changes in two fibres of the proximal pole of a spindle. In the upper fibre the nuclei are swollen and the cytoplasm vacuolated; in the lower fibre the nuclei are drawn

out between the longitudinally disposed fibrillæ. At the equatorial region, because of its peculiar structure, the picture was somewhat modified. The nuclei, already round, seemed first to swell, then to shrink. Their smoothness and sharpness of outline was lost, and they became confluent (figs. 3*a* and *c*). The nucleolus, an intense black spot in the centre of the normal equatorial nucleus (fig. 1*c*) disappeared. And the numbers of the nuclei were greatly diminished (compare figs. 3*c* and 4*a* with 1*c*), seemingly by the process of nuclear fusion. Furthermore, the intrafusal fibres also lost their clarity of outline, so that frequently the cytoplasm of the axial bundle formed a mass in which individual fibres were not distinguishable except by the cords of fused nuclei (fig. 5*b*).

The equatorial region of the spindles was the most resistant to complete degeneration of all the parts of the muscle. However, occasional fibres showed vesicular disintegration of the scanty cytoplasm between the nuclei. And fibrosis, though less obvious, was quite general. This last reaction may be seen in figs. 3*a* and *c* in the best preserved spindle of a fifth interosseous muscle after one year of denervation. In concert with the reduction in size and number of the equatorial nuclei, there was every indication that in the course of time the fibrous transformation would have been completed, as indeed it very nearly was in the spindle shown in fig. 4*a*. Certain it is, however, that were fibrosis complete, the criterion for identifying a structure as a spindle would be destroyed. Although it is not likely that many spindles had suffered this fate, for an average number were still recognizable, it is probable that many individual fibres of the axial bundle had taken this course. For in spindles much altered, but in which fibres were still discernible, these were few in number (fig. 4*a*).

The connective tissues of the spindle reacted to denervation in common with the connective tissues of the remainder of the muscle. In neither case, however, was connective-tissue proliferation excessive until the final stage of fibrotic degeneration had been reached. The spindle capsule first increased slightly in thickness, often at the expense of the periaxial space. Bands of connective tissue, perhaps the original delicate conveyors of nerve fibres, bridged this space. At the poles the capsule closed down gradually on the intrafusal bundle. Thus the periaxial space was encroached on from both ends and narrowed at the middle. Later, the fibrous connections between the capsule and adjacent structures also multiplied. Finally, the capsule became indistinguishably merged in the surrounding fibrotic mass, and a short length of

grossly atrophied or degenerating muscle fibres in a much curtailed periaxial space was all that remained of the spindle. Figs. 4*a* and *b* show, not indeed the final stage of this process, but the last stage giving sufficient contrast of muscle fibre and fibrous tissue for demonstration photographically.

These observations on the results of peripheral nerve lesion apply to the entire group of six cats. Section of the brachial plexus completely denervated the tissues examined. The addition of sympathetic ganglionectomy to this lesion made no appreciable addition to the functional or structural losses in the fore-limb. If sympathetic nerve fibres are sent to the fore-limb by way of the blood-vessels, without an intermediary course in the peripheral nerves, their number is so exceedingly few and their influence so slight that they eluded detection in this study.

Following peripheral nerve lesion, therefore, and in the absence of regeneration, the spindles of skeletal muscle atrophy and degenerate. Furthermore, in the muscles selected for this study, atrophy and degeneration develop along the same lines and with about equal slowness in both extra- and intrafusal muscle. One aspect of this process which was most interesting was the convergence of the various muscle tissues to a common form, with the loss of characterizing features. First, the extrafusal muscle approximated the type of the polar regions of the intrafusal fibre; narrow fibres, central nuclei, coarse striation with equally wide light and dark bands. Later, by loss of striation and increase of nucleation, both came to resemble, sometimes to a confusing degree, the now dispersed equatorial region. The end-product of degeneration for all three tissues was the same—fibrous tissue. It was striking, moreover, that in these processes of decay the equatorial region, which is least differentiated as muscle, retained its character longest. For it was by coming upon equatorial aggregations of nuclei, much reduced to be sure, that the spindles were recognized, in many instances, in an otherwise completely fibrotic mass.

One cannot but speculate, if after a year of denervation extra- and intrafusal muscle are still fragmentarily recognizable as such, how long does muscle tissue maintain its character? And what is more important, should nerve fibres return, for how long a period is the tissue sufficiently preserved to resume its original form and function? Those muscle fibres affected by vacuolar degeneration are obviously completely broken up and removed. But the fibrous process is less destructive. In a region of muscle which on first glance seems completely converted

into tendon, on close inspection faint lines of cross-striation may be observed. Furthermore, the original muscle nuclei and myofibrils, though altered, are still present. And in the spindles vestiges of equatorial aggregation are most persistent. So long, then, as trace of their original structure remains, are these tissues, under proper stimulation, capable of redifferentiation and resumption of function? Or are they, as it were, mere ghosts, incapable of resurrection?

II.—The Trophic Relations of the Components of Innervation to the Muscle Spindle.

The fact has been established that the muscle spindles atrophy and degenerate following peripheral nerve lesion. In order to demonstrate how the components of the peripheral nerve share the responsibility for maintaining the trophic state of the spindle, the three components of such a nerve were now eliminated in turn, each in a group of animals.

The ventral roots, C_6 to T_2 inclusive, were cut on the right side in three cats. By opening the spinal canal, the roots were exposed as they pass laterally to form a spinal nerve. The dorsal roots were gently pulled aside, the ventral roots picked up, clamped and two or three millimetres of the root excised. All these procedures were performed extradurally. The animals were allowed to survive four, six, and twelve months. At the expiration of these intervals they were killed and fixed by injection; and histological preparations were made in the manner described for the peripheral nerve lesions.

The effect of ventral root section on the spindle was characteristic. At the polar regions, atrophy and degeneration developed as in the extrafusal muscle of the same specimen, or as after peripheral nerve lesion, and progressed at approximately the same rate (figs. 6*b*, 7*a* and *c*). The equatorial region, on the other hand, was very much less affected (figs. 6*c* and 7*b*). Degenerative changes seemed, indeed, to be confined to the poles.

At the poles the muscle fibres first became thinner and their nuclei swelled. In animals killed after six months, the cross-striation was noticeably fainter. Connective tissue had begun to obliterate the periaxial space, and at the ends of the spindle fibrous transformation had begun to curtail the length. Occasional fibres, not many, showed vesicular degeneration, and here round cells might be found inside the spindle capsule. After a year of denervation the process of converting the polar regions of the spindle, capsule and muscle bundle into fibrous tissue had progressed far. The majority of the intrafusal fibres showed

vacuolation and segmentation of the cytoplasm with a complete loss of cross-striation and, commonly, of longitudinal fibrillation as well. Figs. 6*b* and 7*a* and *c* illustrate these changes. Uncomplicated fibrous transformation was less common, although the upper fibre of fig. 7*a* shows this process, in contrast with the extreme vacuolation of its lower companion. The over-all length of the spindles was much reduced by shortening at the poles, though the equatorial regions were apparently of normal length (compare fig. 6*a* with 1*a*). This process had gone so far, indeed, in a few spindles that the recognizable portion consisted only of equator.

Standing out from the mass of atrophic or degenerated extrafusal muscle, the equatorial regions were most conspicuous. Enclosed often in much dilated capsules (fig. 6*a*), they were striking objects and seemed to have lost nothing of their normal appearance. On close inspection, however, the fibres composing the intrafusal bundle were perceptibly atrophic. They were thin (fig. 7*b*), and in cross-section the cytoplasm around and between the nuclei was obviously reduced in amount. Yet the individual fibres retained their clarity of outline; the sarcolemma was intact. On the other hand, the nuclei composing the equatorial aggregation appeared normal in every respect. They were round, clear-cut, never confluent, and the nucleoli were typically small and sharp (fig. 6*c*). Furthermore, the arrangement of the nuclei in rows was not disturbed, nor was their number appreciably diminished. The connective tissue encasing the axial bundle seemed slightly increased, but there was no evidence of fibrosis in any part of the muscle fibres bearing nerve fibres. Both the equator aud the variably long regions of accessory sensory innervation—the regions where flower-wreath and club endings occur—seemed to be protected from fibrotic degeneration, and the transition from this region to the poles was often, after a year of denervation, very striking. Against the hazard of vacuolar degeneration, however, the presence of nerve fibres did not afford complete protection. This process, which often affected only one or two of the fibres of an axial bundle, penetrated even into the region of equatorial aggregation, though considerabiy less violently.

In contrast to the differential reaction of the parts of the intrafusal muscle bundle, the capsule of the spindle reacted as a whole. In animals subjected to denervation of four months, when the muscle fibres were still little altered, the capsule commonly appeared thicker from end to end. Heavier connective-tissue strands bound the capsule to adjacent structures and traversed the space between the capsule and the intra-

fusal bundle. In later stages this process completely obliterated the periaxial space at the poles. But at the equator the capsule, while thickened, frequently also became much dilated (fig. 6*a*). Veins, lymphatics and capillaries, particularly those of the spindle, often showed a similar dilatation (figs. 6*a* and *b*), perhaps a mechanical result of the atrophy of the surrounding and supporting muscular tissue.

The dorsal root ganglia, C_6 to T_2 inclusive, were removed on the right side in another series of three cats. The spinal canal was opened laterally as far as the intervertebral foramina. The root ganglia were freed from the ventral roots and excised without opening the dura. Subsequent histological examination of serial sections of these lesions showed that the ganglia were completely removed by this operation, no single cell remaining. However, the operation always entailed slight injury to the superficial layer of ventral root fibres (Tower, 1931). The three animals of this series were also allowed to survive four, six and twelve months. They were then killed and histological preparations were made in the usual way.

The reaction of the spindle to removal of the dorsal root ganglia was in striking contrast to its reaction to ventral root section. In the first place the capsule responded slightly or not at all to the lesion. It became, perhaps, somewhat smaller in diameter and thicker in the region where the bulk of sensory fibres and endings had been removed (fig. 8*a*), but there was no general thickening. The polar regions of the intrafusal muscle bundle likewise seemed unaffected. The muscle fibres were of good size; the nuclei elongated, perhaps unusually so; the cross-striation, intense and clear-cut (figs. 8*b* and *d*). Nerve fibres were present in the usual profusion at the poles, and endings of a very simple motor plaque type were occasionally found.

At the equator, however, the intrafusal muscle bundle exhibited extraordinary modification. Not very noticeably after four months, but quite clearly six months after lesion, the equatorial aggregation had altered. No longer were the nuclei arranged in compact rows, almost filling the sarcolemma. Around and between the nuclei cross-striated sarcoplasm had appeared. By the end of a year of denervation, the volume of cross-striated muscle substance surrounding the equatorial nuclei greatly exceeded the volume of the nuclei (most clearly shown in cross-section in fig. 9*a*). The nuclei, in turn, had become much smaller. And instead of being round and sharply outlined, they were now polygonal or square, or in spindles showing the most intense reaction, elongated and confluent as after peripheral nerve lesions (compare figs. 8*c*

and 3*c*). At the same time the muscle fibres became straighter of outline. All these features are illustrated in figs. 8*a* and *c*. In short, the unique characteristic of the equatorial region, the aggregation of nuclei, was in process of being obliterated, and the region was being converted to the structure of the adjacent polar regions of the spindle.

The sympathetic component of innervation was eliminated on the right side in two cats. From one animal, only the stellate ganglion was removed. This animal was then allowed to live four months. In the second animal, which survived operation one year, the stellate ganglion and cervical sympathetic cord and ganglia were taken out. Both operations seemed to be equally complete in depriving the fore-leg and paw of sympathetic fibres and function.

In contrast with the striking and characteristic results of excluding dorsal and ventral root components from spindle innervation, sympathetic denervation was without perceptible effect. Even so long as one year after the operation, the intrafusal muscle fibres seemed unaltered in any respect. The size, nuclei and striation were quite as in the control material (compare figs. 10*a*, *b* and *c* with 1*b*, *c* and *d*). Nor was the capsule appreciably thicker or thinner. Furthermore, it could not be detected that the number of nerve fibres going to the spindle was at all diminished. Indeed, so far as the spindle was concerned, the sympathetic lesion was inconsequential.

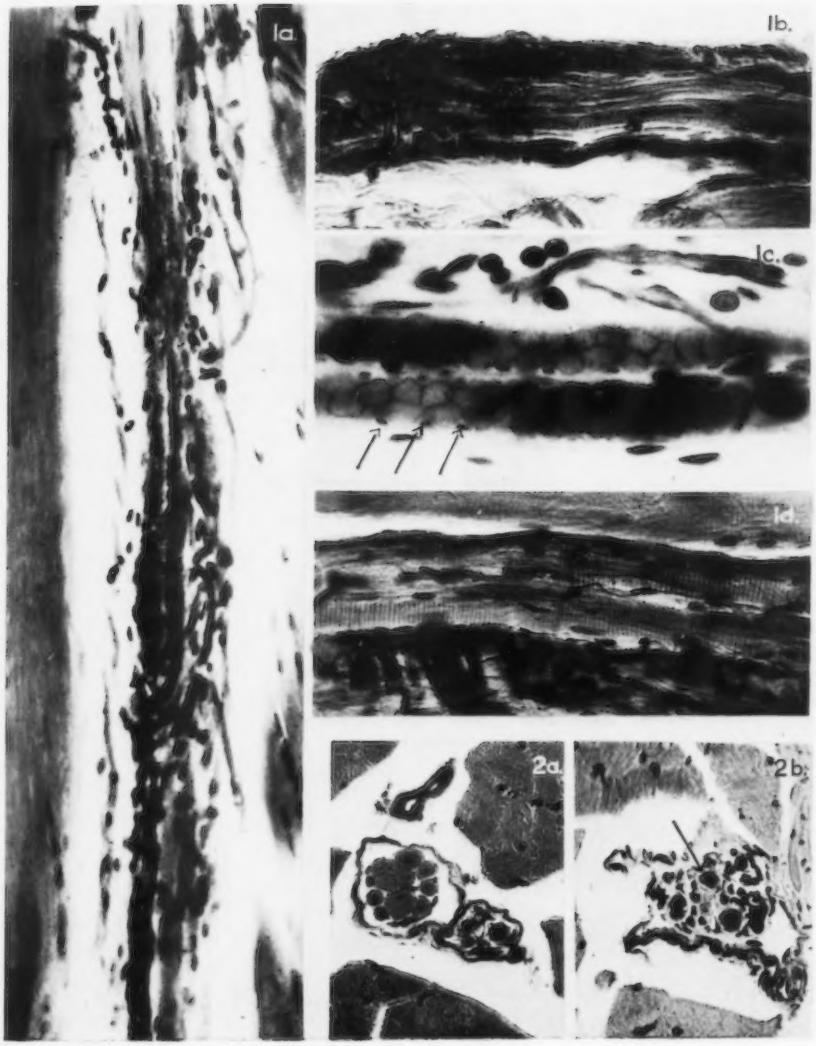
Discussion.

The dorsal and ventral spinal roots share the responsibility for maintaining the muscle spindle in a normal trophic state, as they share its innervation. The sympathetic nervous system, which enters into the spindle probably only in a vasomotor capacity, does not participate in this function. So much is clear. But the manner in which the spinal roots share control is less obvious. The beneficent effect of one intact innervation is not transmitted throughout the cell. Rather, at first glance, it seems to be locally exercised over that portion of the spindle where its nerve endings predominate. From another point of view, however, the atrophy attending root lesions was less spatially distributed than functionally. Those structures of the intrafusal muscle fibre differentiated for a certain function, atrophied when that function fell into disuse through denervation. And subsequently, the portions so affected, degenerated. Thus, after motor-root section, the polar regions showed the greatest atrophy, but it was not so much the polar regions, as the contractile substance, the cross-striated substance, which was

reacting. Even at the equator this material was perceptibly reduced, even degenerated, and only the equatorial aggregate of nuclei, which cannot be conceived of as contractile, was unaffected. Following sensory denervation, on the other hand, this nuclear aggregation was shrunken and dispersed, and the cross-striated substance increased. The contractile structure was, as it were, usurping the entire fibre.

If our surmise is correct, that the annulo-spiral ending is an organ excited by the action currents of the intrafusal muscle fibres, it might be argued that ventral root section would abolish together both the motor and sensory functions of the spindle. However, the spindles occurring in the cat's interosseous muscles are complex sensory organs, although all spindles, those of the frog for example (Hines, 1931), are not. Besides the annulo-spiral ending, which appears to be the organ responding to active contraction and responsible for proprioceptive inhibition, there are other clearly-defined sensory structures. The flower-wreath endings (second order endings of Ruffini) and the knob-like endings resemble organs found in the intramuscular and subcutaneous connective tissue. They suggest structures reacting to passive disturbance. It is possible that these are the afferent organs of the stretch reflex. Moreover, free terminals of finely myelinated or unmyelinated nerve fibres are also present. Even in the failure of active contraction, these latter varieties of sensory ending may still function. And thus their host tissue, the intrafusal fibre, may be preserved from the regressive changes of disuse.

The effect of sensory denervation on the spindle is, however, not so simply explicable. The sensory endings of the spindle are generally considered to be epilemmal; closely applied to the surface of the muscle fibre but not penetrating into its substance. The aggregation and form of the equatorial nuclei suggest a region of extraordinarily high metabolism under the lead-off of the spiral ending. This region is presumably activated through motor nerve endings situated toward the poles, and the sensory nerve endings by it in turn. What sort of influence, then, is exerted, antidromically as it were and across two cell surfaces, by the sensory endings on the muscle? The changes in this region following sensory denervation would seem to be in a class with transneuronal degeneration in the central nervous system. If this is atrophy of disuse, one is led to wonder how the spindle would react to section of the dorsal roots proximal to the ganglion. The loss of function for the animal as a whole would be the same, yet there would be no physical degeneration of nerve tissue contiguous to muscle.



All figures on this and the following plates are untouched photomicrographs. All except figures 1*d* and 6*a* are contact prints, and the sizes of objects taken with the same objective and ocular, are comparable. Figures 1*a* and 6*a* were enlarged × 2. Apochromatic objectives and compens oculars were used throughout.

Normal spindles in the left fore-leg of cat S IIe.

FIGS. 1*a-d*.—Spindle from the fifth interosseous muscle. (*a*) Central region of spindle under low magnification, taken to show the width and thickness of the capsule and intrafusal muscle bundle. The sensory innervation enters from the left. 8 mm. objective, × 7 ocular. (*b*) Proximal pole of the same spindle, showing a nerve ending of the motor type. 4 mm. × 10. (*c*) Detail under oil, of the equatorial region of fig. 1*a*. The arrows indicate the annulo-spiral nerve ramifications cut across. 2 mm. × 10. (*d*) Distal pole of the same spindle, showing the coarse striation characteristic of spindle muscle. 4 mm. × 10.

FIGS. 2*a* and *b*.—Spindle from the fourth interosseous muscle. (*a*) Pole, 1 mm. proximal to the maximum equatorial development. 4 mm. × 10. (*b*) Maximum equatorial development. Arrow indicates a nerve ramification embedded in the cytoplasm of the muscle fibre. 4 mm. × 10.

To illustrate paper by Sarah S. Tower.

Spindles in the right leg of cat S IIe, killed one year after section of the right brachial plexus.

FIGS. 3*a*-*c*.—The most normal appearing spindle remaining in the fifth interosseous muscle. (*a*) Equatorial region, showing reduction in size of the nuclei, and fibrous degeneration; the latter, especially clear at the lower end. 4 mm. × 10. (*b*) Proximal pole, showing vacuolar degeneration in the upper fibre, and fibrosis in the lower. 4 mm. × 10. (*c*) Detail of the equatorial region under oil, showing the changes in the nuclei, especially confluence. 2 mm. × 10.

FIGS. 4*a* and *b*.—Spindle from the same muscle showing more advanced degeneration. (*a*) Equatorial region, showing extreme reduction of the nuclei. 4 mm. × 10. (*b*) Proximal pole, muscular tissue completely degenerated; nothing but capillaries and fibrous tissue remaining. 4 mm. × 19.

FIGS. 5*a* and *b*.—Spindle from fourth interosseous muscle. (*a*) Pole 1 mm. proximal to maximal equatorial development, fairly well preserved. 4 mm. × 10. (*b*) Maximum equatorial development showing, in cross-section, the condition shown in 3*c*. 4 mm. × 10.

To illustrate paper by Sarah S. Tower.

Spindles from the right fifth interosseous muscle of cat S XIc, killed one year after section of the right ventral roots C_6 to T_2.

FIGS. 6*a-c*.—Spindle with intact equatorial innervation but no polar innervation. (*a*) Central region of spindle under low magnification, taken to show the enormously dilated and thickened capsule, and the sensory nerve fibres. (*b*) Proximal pole of the spindle, showing advanced degeneration of the muscle fibres, total loss of cross-striation and segmentation. The greatly dilated capillary tuft in the corner is also characteristic. 4 mm. × 10. (*c*) Detail under oil of the equatorial region, to show the well-preserved nuclei with sharp nucleoli. 2 mm. × 10.

FIG. 7*a-c*.—Spindle presenting more severe alteration. (*a*) Proximal pole, showing an extreme degree of vacuolar degeneration in the lower muscle fibre, with a fibrous process in the upper. 4 mm. × 10. (*b*) Equator, showing general atrophy, but intact nuclei and nucleoli. 4 mm. × 10. (*c*) Distal pole, showing degeneration. 4 mm. × 10.

To illustrate paper by Sarah S. Tower.

FIGS. 8*a-d*.—Spindle from the right fifth interosseous muscle of cat S VIId, killed one year after excision of the right dorsal root ganglia C_6 to T_2. (*a*) Equatorial region, showing the reduction in number and size and confluence of the nuclei, and the presence of cross-striated muscle substance continuously throughout this region. 11 mm. × 10. (*b*) Distal pole showing clear-cut cross-striation. 4 mm. × 10. (*c*) Detail of equator under oil, showing the nuclear changes—shrinkage, elongation and confluence. 2 mm. × 10. (*d*) Proximal pole. 4 mm. × 10.

FIGS. 9*a* and *b*. Same animal, spindle from fourth interosseous muscle. (*a*) Maximum equatorial development, showing the great quantity of cytoplasm around the much reduced nuclei. Compare with 2*b*. 4 mm. × 10. (*b*) Pole 1 mm. distal to maximum equatorial development. 4 mm. × 10.

FIGS. 10*a-c*. Spindle from the right fifth interosseous muscle of cat S Vc, killed one year after removal of the right stellate ganglion and cervical sympathetic chain. (*a*) Proximal pole; quite normal. 4 mm. × 10. (*b*) Detail of equatorial nuclei under oil. 2 mm. × 10 (*c*) Distal pole, also quite normal. 4 mm. × 10.

To illustrate paper by Sarah S. Tower.

Moreover, it may be questioned if the annulo-spiral ending is in reality epilemmal. In the equatorial region the muscle fibre loses the clear-cut contour which is conferred on the polar regions by a well-developed sarcolemma. The subdivision of the fibres at the equator may be an expression of this lack of a containing membrane. Repeatedly, in sections through equatorial regions, the finer ramifications of the annulo-spiral ending appeared to be embedded in the sarcoplasm of the muscle fibre (fig. 2*b*—arrow). Particularly was this true in the angles or chinks between nuclei where there was an accumulation of cytoplasm. In figure 1*c*, such fine ramifications are seen cut across, as fine black dots along the borders of both of the muscle fibres. It is possible, of course, that the embedding of the nerve fibres in the muscle fibre was an artifact of fixation. However, recent studies, in particular those of Heringa (1920), have emphasized the exceedingly intimate relationship of sensory nerve endings, as well as motor, to peripheral non-nervous structures. Should it prove to be true that the annulo-spiral ending is intra-cytoplasmic, then, in the close structural and functional association of the nervous and non-nervous elements in the sensory ending, a subtle metabolic reciprocity may so operate that the peculiar form of one of the tissues is maintained, as perhaps it was originally developed, only in the presence of the other tissue, and the inadequate concept of disuse atrophy need not be invoked.

That such is not also the mechanism of degeneration following motor denervation, remains to be proven. In a previous study (Tower, 1931) the author has pointed out that sensory denervation of the cat's fore-limb, which greatly reduces the use of the limb musculature, leads to no appreciable atrophy. Certainly it entails no degeneration. For degeneration a motor lesion is essential. The distribution of the regressive changes in muscle following root lesions may be an exposure, not of the extent of the tissue falling into disuse, but of the actual extent of a syncytial structure of nerve and muscle. A physical representation of this is afforded by the apparent continuity of the neurofibrillæ through the periterminal net with the anisotrophic discs of the muscle fibre. Such pictures, as well as the seemingly intracellular position of the annulo-spiral ending, may well be artifacts of fixation in their clarity. But it is scarcely to be doubted that they express a true condition of protoplasmic continuity of nerve and muscle. In disturbance of the metabolic relationships of two tissues so closely interwoven, both physically and functionally, a more convincing basis or the profound disorder following denervation is to be found than in the more simple concept of disuse.

SUMMARY.

In a series of fourteen young adult cats four varieties of lesion were produced: peripheral nerve section, ventral root section, dorsal root, and sympathetic ganglion excision. Four, six or twelve months later, the animals were killed and Bielschowsky silver preparations of muscle made. The muscle spindles of the fifth and fourth interosseous muscle were counted and carefully studied.

Following peripheral nerve lesions the spindle muscle reacted virtually in the same manner and in the same time as did the extrafusal muscle. The fibres shrank; the nuclei swelled; the cross-striation faded; the longitudinal deepened, and the end-product was fibrous tissue. The capsular connective tissues also increased.

With ventral root section the polar portions of the spindle atrophied and degenerated, and the capsule thickened. After removal of the dorsal root ganglia, the reaction was confined to the equatorial region of the muscle fibres. Sympathetic denervation was without effect on the spindle fibres or capsules.

These findings are analysed from the point of view of disuse atrophy, but their possible interpretation on the basis of a metabolic interdependence of nervous and non-nervous tissues is discussed.

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INORGANIC CONSTITUENTS OF THE CEREBROSPINAL FLUID.

III.—Magnesium and Calcium in Meningitis.

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Introduction.

More magnesium is normally present in the cerebrospinal fluid than in the serum or plasma of the blood taken at the same time. Cohen [1], Stary, Kral and Winternitz [12], and McCance and Watchorn [8] have each established this fact independently in more than 120 cases, rather over half of which were reported by McCance and Watchorn. Unlike the cerebrospinal fluid, œdema fluid has always been found to contain *less* magnesium than the corresponding serum (Magnus Levy [7], Salvesen and Linder [11]), and this is also true of the ocular fluids (Duke Elder [3, 4], Tron [14]). Ultrafiltrates have also been found to contain less magnesium than their sera (Tschimber and Tschimber [15], Stary and Winternitz [13], Watchorn and McCance [17]), and the magnesium found in œdema and ocular fluids can be satisfactorily explained on the basis of ultrafiltration. It is certain, however, that the magnesium in the cerebrospinal fluid cannot be so explained.

In addition to finding more magnesium in the cerebrospinal fluid than in the serum, Cohen [1] found that the cerebrospinal fluid magnesium was very constant in amount (average 3·28 mgm. per 100 c.c.), and that an intramuscular injection of a magnesium salt which greatly increased the serum magnesium for a short time did not raise the magnesium in the cerebrospinal fluid. McCance and Watchorn [8] confirmed this relative constancy of the cerebrospinal fluid magnesium (average 3·33 mgm. per 100 c.c.) and found that this was maintained with pathological serum values ranging from 2·0 to 4·05 mgm. per 100 c.c. (normal: 2·35 to 2·65 mgm. per 100 c.c.).

Among his series of eighteen cases, Cohen recorded two cases of

tuberculous meningitis in which the cerebrospinal fluid contained less than the normal amount of magnesium. One contained rather less than the serum (in mgm. per 100 c.c.) and the other almost the same amount. Stary, Kral and Winternitz [12] also recorded two cases of tuberculous meningitis, in which the serum value equalled or slightly exceeded a low cerebrospinal fluid value. They analysed, however, three other fluids in which the magnesium was as low or lower than in the tuberculous ones. And although they found in general that the magnesium in the cerebrospinal fluid bore no relationship to the serum, yet they concluded on the basis of two cases that a serum magnesium greater than the cerebrospinal fluid magnesium was characteristic of tuberculous meningitis.

Eisler [5] found the magnesium in the cerebrospinal fluid constantly raised in meningitis, but all his figures are so low that his results must be accepted with reserve.

The calcium in the cerebrospinal fluid has been very much more studied than the magnesium. The literature has been so well summarized by Critchley and O'Flynn [2] and Walter [16], and to a lesser extent by Stary, Kral and Winternitz [12], that it is unnecessary to do so here. It is still uncertain whether ultrafiltration alone under all conditions can explain the calcium found in the cerebrospinal fluid. Merritt and Bauer [9] have concluded that it can, but Watchorn and McCance [17], who have discussed this point recently, have advanced experimental and other evidence that this simple explanation may not be sufficient to cover all the observed facts.

Source of Materials and Technique.

Most of the material has been obtained from the general and children's wards of King's College Hospital, but some has been obtained from the Belgrave Hospital for Children and some from St. Giles' Hospital. A few isolated cases have been obtained from other centres. The taking of the blood and cerebrospinal fluid and the analytical technique were fully described by McCance and Watchorn [8], and need not be repeated here. The blood has always been withdrawn before the cerebrospinal fluid, since Cohen has stated that lumbar puncture may raise the serum magnesium. The figures given for chlorides have been taken from the routine King's College Hospital records, or, if the material was obtained elsewhere, determinations were, if possible, specially made by the same method (i.e., direct titration of the cerebrospinal fluid with silver nitrate, using pot. chromate as indicator).

Results.

Table I contains all the experimental results. The diagnosis (column 3) has been accepted (i) if post-mortem confirmation was obtained; (ii) if organisms were seen in direct smears of the cerebrospinal fluid or grown therefrom, and if the clinical findings and course were in agreement. In a number of cases it has not been possible to obtain blood with the cerebrospinal fluid.

Discussion of the Results.

Of the 65 cases of general and neurological diseases reported by McCance and Watchorn, only 4 had cerebrospinal fluid magnesium values below 3·00 mgm. per 100 c.c., and only 2 of these were below 2·95 mgm. per 100 c.c. The lowest was 2·83 mgm. per 100 c.c. Of the present series of 33 cases of meningitis covering 46 separate samples of cerebrospinal fluid, only 21 of the latter were over 3·00 mgm. per 100 c.c., and only 6 of these were above the average non-meningitic figure (3·33 mgm. per 100 c.c.). Fifteen were below 2·83 mgm. per 100 c.c. It is quite evident therefore that the cerebrospinal fluid magnesium tends to fall in meningeal inflammation. On making a closer analysis, it is further apparent that:—

(1) None of the *acute* cases, whether meningococcal, *B. friedländer*, pyogenic or pneumococcal in origin, showed a fall. If therefore these are excluded from the general average, practically all the cases of chronic meningitis, whatever the infecting organism, had less magnesium than normal in the cerebrospinal fluid—some of them very much less.

(2) There was a definite tendency for the fall in chlorides and magnesium to run parallel with each other. Thus:—

Chlorides as NaCl mg. per 100 c.c.		Number of cases		Mg. average mg. per 100 c.c.
Below 640	..	10	..	2·49
640-689	..	18	..	2·95
690 and over	..	9	..	3·31

This relationship is evident, not only statistically but also in most individual cases. Case 27 is an exception. No case with chlorides greater than 700 mgm. per 100 c.c. showed any fall in magnesium.

(3) In the only case (No. 24) which recovered and on whom a series of lumbar punctures was obtained, the magnesium fell during the chronic phase of the disease to rise again to normal during recovery.

(4) The serum magnesium *did not fall* with the cerebrospinal fluid magnesium. The average of the 24 sera was 2·96 mgm. per 100 c.c.

This is well over the upper limits of normal, but agrees very closely with the average of the large series of hospital patients studied by McCance and Watchorn (2·90 mgm. per 100 c.c.). Meningitis therefore appeared to have no specific effect on the *serum* magnesium.

(5) The serum calcium averaged 10·1 mgm. per 100 c.c. and the corresponding cerebrospinal fluids 5·84 mgm. per 100 c.c. These figures may be compared with 10·7 and 5·8 mgm. per 100 c.c., respectively, taken from McCance and Watchorn's series of other non-meningitic diseases. The meningitic $\frac{\text{C.S.F.}}{\text{serum}}$ ratio was 0·577 and the non-meningitic 0·543. These differences are scarcely significant, but they tend to show that relative to the serum there was slightly more calcium in the cerebrospinal fluid in meningitis. Merritt and Bauer [9] found much greater differences between meningitic and non-meningitic cases, and their explanation that the increase of calcium in the meningitic fluids was due to increased capillary permeability may be the correct one. Even in Merritt and Bauer's series, however, all the individual cases did not conform, and there is probably another factor to be considered besides the increased permeability of the choroid plexus to proteins [17].

General Discussion.

(1) *Practical significance and diagnostic value.*—It is evident in this series of cases that a fall in the cerebrospinal fluid magnesium has been the rule in chronic meningitis. A knowledge of the amount of magnesium in the cerebrospinal fluid therefore in any given case should be a test of diagnostic value; how valuable, only an extended trial can determine. Meanwhile it is only possible to suggest that (i) a fall in the cerebrospinal fluid magnesium is not peculiar to any one type of meningitis; (ii) so far a fall has never been observed in an acute case; (iii) the return to normal or towards normal may be of prognostic significance (Case No. 24); (iv) at present a fall in magnesium appears to have somewhat the same significance as a fall in chlorides, and as the determination of chlorides is much easier than that of magnesium, no one would willingly replace the former by the latter if only one chemical test were to be made.

(2) *Theoretical significance.*—On four carefully studied cases, Linder and Carmichael [6] have shown that the fall in chlorides in the cerebrospinal fluid is accompanied by a fall in the plasma chlorides, so that the normal $\frac{\text{C.S.F.}}{\text{serum}}$ ratio remains unchanged. There appears at

present no prospect of explaining the fall in magnesium on similar simple lines. It is in fact very difficult on physico-chemical grounds to explain why the fall in an anion (Cl) should be accompanied by a fall in a kation (Mg) which relative to the Cl ion is present in insignificant amounts. The parallelism may be entirely fortuitous. It is unwise at present to attempt to explain any movements in cerebrospinal fluid magnesium in the light of an alteration of permeability affecting a "Donnan" membrane equilibrium (1), for the magnesium normally found in the cerebrospinal fluid cannot be so explained. Stary, Kral and Winternitz [12] have suggested that the magnesium in the cerebrospinal fluid is normally above the serum because the extra magnesium diffuses in from the surrounding brain matter. This is not a satisfactory explanation because: (i) When the serum rises very high the cerebrospinal fluid does not follow, but tends to remain constant. One would not expect this if the cerebrospinal fluid magnesium were made up of the sum of the ultrafiltrable serum magnesium and the magnesium leaking in from the brain tissue. (ii) It is difficult to understand why in meningitis less magnesium should diffuse into the cerebrospinal fluid than before.

Collecting together all the evidence of Cohen [1], Stary, Kral and Winternitz [12], McCance and Watchorn [8], and Watchorn and McCance [17], it is difficult to escape from the conclusion that the magnesium in the cerebrospinal fluid is normally fixed at a definite level by some active cellular process. This is not in any way antagonistic to the view that the *total* concentration of electrolytes in the cerebrospinal fluid is governed by a process of physical diffusion [10], for compensatory changes will take place in the freely diffusible ions so that thermodynamical equilibrium with the plasma is attained. On the above basis the meningitic changes may be explained either: (1) As a partial loss by the active cells of their power to fix the cerebrospinal fluid magnesium at a constant level. Local toxæmia might cause this loss. The cerebrospinal magnesium would then tend to take up its ultrafiltration level, and would show a fall unless the serum magnesium were very high indeed [17]. (2) As an alteration in the level at which the cellular process stabilizes the fluid magnesium. This seems the more probable of the two. Case No. 1, with serum magnesium 3·81 mgm per 100 c.c. and fluid magnesium 2·90 mgm. per 100 c.c., gave from the serum an ultrafiltrate containing 3·38 mgm. per 100 c.c. This is outside the experimental error of the method [17] and shows that in this case, at any rate, the fluid magnesium was being maintained *below* the ultrafiltration level.

TABLE I.

No.	Age	Diagnosis	MAGNESIUM		CHLORIDES	CALCIUM		Remarks
			Serum mg. per 100 c.c.	C.S.F. mg. per 100 c.c.	C.S.F. mg. per 100 c.c.	Serum mg. per 100 c.c.	C.S.F. mg. per 100 c.c.	
1	6	Tuberculous meningitis	3·81	2·90	660	12·03	5·63	–
2	2¾	,,	3·51	3·37	692	10·85	6·38	Very early case
3	11	,,	3·17	2·61	600	9·51	5·59	–
4	–	,,	3·2	2·35	610	9·61	5·20	–
5	13	,,	3·89	2·98	610	10·68	5·59	–
6	1¼	,,	2·61	2·88	–	11·06	4·84	–
7	1¾	,,	3·64	3·11	666	12·50	7·90	–
8	1 1/12	,,	2·86	2·44	620	9·70	6·10	–
9	7⅓	,,	2·94	2·74	652	9·31	4·16	–
10	6	,,	2·97	2·91	665	8·81	5·35	Material collected 15.6.31
			–	2·91	672	–	5·94	,, ,, 16.6.31
11	26	,,	2·75	2·37	595	9·90	5·10	,, ,, 27.6.31
			2·42	2·21	575	9·50	6·00	,, ,, 28.6.31
			2·88	2·47	620	9·80	–	,, ,, 30.6.31
12	5	,,	3·01	3·06	680	10·39	5·78	Diagnosis not proved. No p.m.
13	36	,,	3·33	2·68	680	9·11	6·37	Material collected 16.10.31
			3·31	2·94	640	8·72	6·57	,, ,, 20.10.31
14	20	,,	3·14	2·50	610	10·09	6·86	–
15	15	,,	2·67	3·11	700	10·29	5·59	Material collected 30.10.31
			2·59	2·85	680	9·11	5·39	,, ,, 3.11.31
16	–	,,	–	2·88	650	–	7·98	–
17	7/12	,,	–	3·11	640	–	4·02	–
18	3½	,,	–	2·66	640	–	4·85	–
19	38	,,	–	2·78	670	–	6·90	–
20	13	,,	–	3·21	690	–	5·98	Diagnosis not proved. No p.m.
21	2 7/12	,,	–	3·08	640	–	5·39	Material collected 7.9.31
			–	3·08	–	–	5·29	,, ,, 8.9.31
			–	3·08	–	–	–	,, ,, 10.9.31
22	1	Pneumococcal meningitis	3·16	2·54	620	12·08	7·62	Chronic case. Material collected 1.6.31
			–	2·58	680	–	7·03	Material collected 6.6.31
			–	2·46	620	–	5·84	,, ,, 12.6.31
23	–	,,	–	3·47	–	–	4·61	Acute case
24	¾	,,	–	3·42	690	–	6·58	Chronic course. Material collected 5.6.31
			–	3·19	–	–	5·69	Material taken 6.6.31
			–	2·82	–	–	5·54	,, ,, 10.6.31
			–	3·42	670	–	4·95	Recovering. Material taken 13.6.31
25	5	,,	–	3·11	709	–	5·30	–
			–	3·14	–	–	5·60	–
26	–	,,	–	3·00	–	–	5·59	–
27	1¾	Streptococcal meningitis	3·62	3·68	640	10·09	5·10	–
28	–	*B. friedländer* meningitis	–	3·33	–	–	4·85	–
29	–	Probably pyogenic	–	3·32	770	–	7·23	Diagnosis uncertain. Acute onset. No p.m.
30	8	Pyogenic meningitis	2·52	3·33	722	10·10	–	Following bilateral mastoid infection
31	–	,,	4·64*	2·91	665	10·69	5·15	Chronic course; secondary to infected mastoid
32	1/3	Meningococcal meningitis	3·19	3·59	760	10·39	7·35	–
33	12	,,	3·28	3·32	756	8·72	5·29	Quoted from McCance and Watchorn, *Quart. Journ. Med.*, 1931, **24**, 371

* Serum slightly hæmolysed, omitted from averages.

SUMMARY.

(1) In chronic meningitis (tuberculous or pneumococcal) subnormal amounts of magnesium have been found in the cerebrospinal fluid. A fall has not been observed in the acute cases.

(2) The fall in the magnesium in meningitis has been found roughly to run parallel with the well-known fall in chlorides.

(3) In one case which recovered the cerebrospinal fluid magnesium returned to normal.

(4) The determination of cerebrospinal fluid magnesium should be of diagnostic value.

(5) The cerebrospinal fluid calcium showed little, if any, significant change in meningitis.

(6) The theoretical significance of these results has been discussed.

We wish to express our thanks to all those who have in any way helped us to obtain material for this work.

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TONIC PUPILS AND ABSENT TENDON REFLEXES: A BENIGN DISORDER *SUI GENERIS*; ITS COMPLETE AND INCOMPLETE FORMS.

BY W. J. ADIE.

THE tonic pupillary reaction (syn. pupillotonia, myotonic convergence reaction, tonic convergence reaction of pupils apparently inactive to light) has been known to ophthalmologists since 1902 when Saenger and Strasburger described it independently.

Last year, under the title "Pseudo-Argyll Robertson pupils with absent tendon reflexes: a benign disorder simulating tabes dorsalis." I gave an account of five cases in which I found typical tonic pupillary reactions associated with loss of some or all of the deep reflexes in the upper and lower limbs. In the meantime I have seen eight more of these cases. I have found, too, mainly in journals devoted to ophthalmology, reports of forty-four cases presenting the tonic pupillary reaction; in nine of these absence of reflexes is recorded.

I use these twenty-two cases to establish the existence of the disorder I am about to describe in what I call its complete form. It is characterized by the presence of the tonic pupillary reaction in its most characteristic form and absence of one or more of the tendon reflexes.

Since 1878 when Jonathan Hutchinson introduced the term ophthalmoplegia interna many papers have appeared on this subject giving series of cases with analyses according to the supposed cause. In every series there is a large group in which the cause of the eye signs was unknown; twelve of Uhthoff's thirty cases are included under this heading. I suggest that most of these cases of "ophthalmoplegia interna unilaterale" in otherwise healthy young patients are examples of the disorder that concerns us here. I base this synthesis on my interpretation of the pupillary signs. According to this interpretation the "iridoplegia" or "ophthalmoplegia interna" in these cases represents a phase of the tonic pupil that may either precede the appearance of typical tonic reactions, or appear as an exacerbation in a pupil that had previously presented tonic reactions. Cases of this kind will be referred to as incomplete forms of the disorder.

Author	Year	Sex	Age	Reflexes	Blood and c.s.f.	Author's remarks
Nonne	1902	M.	40	A.Jerks absent R. and L.	—	No evidence of syphilis. Loss of ankle-jerks due to diabetes
Marcus ..	1906	M.	12	K.J. absent R. and L.	—	The signs "might be considered sufficient evidence of congenital syphilis. I am, however, inclined to take a less serious view"
Oloff .. 1	1914	M.	18	K.J. absent R. and L.	Blood negative; c.s.f. normal	No comment
2	1914	M.	44	K.J. absent R. and L.	—	As yet no other signs of tabes or G.P.I.
Jess	1914	M.	21	Right A.J. absent	Blood negative	No comment
Lerperger ..	1914	M.	32	No details ..	—	Neurological examination suggests incipient tabes
Axenfeld ..	1919	F.	19	Triceps, K.J. and A.J. absent R. and L.	Blood once suspicious, once negative	Probably congenital lues
Gehrcke ..	1921	F.	45	A.J. absent R. and L.	Blood negative; c.s.f. normal	Seems to be a case of imperfect stationary tabes
Behr	1921	F.	55	A.J. absent R. and L.	Blood negative: c.s.f. normal	Organic nervous disease may be excluded
Weill and Reys	1926	M.	26	K.J. feeble, A.J. absent R. and L.	Blood negative; c.s.f. normal	Signs attributable to polyneuritis after rheumatic fever or influenza
Foster Moore 1	1931	F.	49	K.J. absent, R. and L.	—	Not in any way related to syphilis
2	1931	F.	16	K.J. very sluggish, R. greater than L.	—	—
Adie .. 1	1931	F.	36	All reflexes absent	Blood negative; c.s.f. normal	A benign disorder *sui generis*; no relation to syphilis
2		F.	23	K.J. and A.J. absent R. and L.	Blood negative; c.s.f. normal	—
3		M.	32	All absent ..	Blood negative; c.s.f. normal	—
4		F.	17	K.J. brisk R. and L.; A.J. very sluggish R. and L.	Blood negative; c.s.f. normal	—
5		F.	45	A.J. absent R. and L.	Blood negative; c.s.f. not examined	—
New cases— 6		F.	43	K.J. and A.J. absent R. and L.	Blood negative; c.s.f. normal	—
7		F.	24	K.J. brisk R., absent L.; A.J. sluggish R., absent L.	Blood negative; c.s.f. normal	—
8		F.	35	K.J. and A.J. absent R. and L.	Blood negative; c.s.f. normal	—
9		F.	18	All absent ..	Blood negative; c.s.f. normal	—
10		F.	50	K.J. and A.J. absent	Blood negative	—
11		F.	31	K.J. brisk R., absent L.; A.J. absent R., sluggish L.	Blood negative	—
12		F.	17	A.J. absent R. and L.	Blood negative	—
13		F.	23	A.J. absent R. and L.	—	—

Every experienced neurologist has seen a few patients with absence of the tendon reflexes for which no cause could be found. Acting on the suggestion of Dr. James Collier, I mention these cases here and submit that some of them are incomplete examples of this disorder. For proof I await a case in which a tonic pupil appears under observation.

If my views are correct the disorder I am describing may manifest itself in the following forms :—

(1) The complete form—typical tonic pupil and absence of reflexes.

(2) Incomplete forms: (*a*) tonic pupil alone; (*b*) atypical phases of the tonic pupil alone ("iridoplegia"; "internal ophthalmoplegia"); (*c*) atypical phases of the tonic pupil with absent reflexes; (*d*) absent reflexes alone.

The Tonic Pupil.

In its most characteristic form the tonic pupil is usually unilateral and almost always larger than its normal fellow; it is never miotic.

When the usual bedside methods are used the reaction to light, direct and consensual, appears to be completely or almost completely absent; after a sojourn in a dark room for an hour or so the pupils dilate to an equal size; thereafter, on exposure to bright diffuse daylight, the abnormal pupil, perhaps after a short delay, contracts slowly; this contraction may continue until the pupil becomes smaller than it was before it dilated in the dark; it then, again after a short delay, dilates to its original size. The most important feature of the tonic pupil is its behaviour on convergence. If the patient fixes a near object and continues to gaze at it intently the pupil, sometimes after a delay of several seconds, contracts slowly and with increasing slowness through a range often greatly in excess of the normal; contraction down to pinhead size is not uncommon; the larger abnormal pupil then becomes smaller than its fellow. After the effort to converge is relaxed the pupil continues to contract, or remains fixed for a few seconds, or begins to dilate slowly again at once; dilatation once begun proceeds at a slower rate than contraction, so that many seconds or several minutes may elapse before it reaches its original size. Accommodation may be affected in the same manner; the defect is noticed most often during relaxation; after fixation of a near object some seconds elapse before distant objects become clear. There is no constant relation between the rate of contraction of the iris on convergence and of the ciliary muscle during accommodation in the same case (Axenfeld).

The same slow dilatation can sometimes be observed after the pupil has contracted on forcible closure of the lids (tonic lid-closing reaction).

The tonic pupil dilates fully and promptly to mydriatics and contracts under eserine.

In nineteen cases that I have examined myself, the abnormal signs were unilateral in fourteen.

There are very few exceptions to the rule that the abnormal pupil is the larger one. I have seen one example and I know of two others (Oloff, Domarus). It may be regularly or irregularly oval with its long axis vertical or horizontal. The pupil often varies in size through a considerable range during the day; it is often at its smallest in the morning; two patients said that a pupil, usually widely dilated, became quite small after they had been crying (probably a tonic lid-closing reaction). Behr states that he saw "ausgesprochener Hippus" confined to the abnormal pupil in three of his cases. In one of Oloff's cases the signs were found now in one eye, now in the other; the abnormal pupil was always the larger one. This is an unique observation. The findings, however, often vary considerably in the same eye at different examinations.

In most of my cases I have been able to confirm the observations that the pupil dilates in the dark (Dimmer), and then contracts in diffuse daylight (Lerperger), sometimes to a size smaller than it was before (Behr). In some of them, however, I obtained no response. In two of my cases with bilateral tonic convergence reactions the response differed in the two eyes on exposing them to light after an hour in the dark room. In one case one pupil contracted slowly and remained small; in another, one pupil contracted, but in this case the response was prompt and not maintained. In both instances the pupil that reacted to light was usually smaller than its fellow and it had varied in size from time to time.

Relaxation after convergence always proceeds much more slowly than the tonic contraction. In a large majority of the cases the pupil remains small for several or many seconds before it begins to dilate again. Contraction and relaxation are slowest, always I think, towards the end of the movement. I know of only one exception to the rule that both movements are always affected. In one of Marcus's patients, contraction on convergence was normal, but dilatation was very slow.

Some of these patients have difficulty in sustaining the act of convergence. If they are not encouraged to persist the presence of the tonic contraction may easily be missed. Repetition does not facilitate movement as it often does in myotonic muscles.

Tonic accommodation is mentioned in but a small proportion of the cases. It has never been observed as an isolated sign.

The foregoing paragraphs deal mainly with the typical tonic pupil in which all movements, though tardy, are normal or excessive in range.

I must now deal with cases that are, according to my view, certainly examples of the same disorder, but have been reported without any reference to the tonic pupillary reaction.

Under the title "Non-luetic Argyll Robertson pupil," Foster Moore has reported fifteen cases characterized by "the complete or substantially complete inaction of the pupil to the light stimulus, the leisurely manner in which it contracts with convergence and in which it again dilates after relaxation of convergence; the frequency with which it is unilateral; the integrity of accommodation; the absence of syphilis; the presence of knee-jerks and the absence of signs of any nervous disease even after many years." His clear description of the pupillary phenomena leaves no room for doubt that he was observing what I call here the tonic pupillary reaction. In most of his cases the condition was discovered in the course of a routine examination; accommodation was defective in one case only. In most of them the knee-jerks were present, in one they were lost; in another they were obtained on reinforcement only. It may be that the arm and ankle jerks were not tested in every case.

Mr. Foster Moore made it possible for me to see several of his patients and he kindly allowed me to read the notes of his unpublished cases. Without any hesitation I conclude that some of them are complete and the remainder incomplete examples of the disorder I have described.

Somewhat more aberrant are the cases in which the abnormal pupillary signs were designated by the terms iridoplegia, internal ophthalmoplegia or fixed pupil.

In the cases of "ophthalmoplegia with absent tendon reflexes," described by Morgan and Symonds, the pupils were said to be either fixed or very sluggish to light and on convergence.

These authors refer to the cases described by Foster Moore, and state that theirs differ from his in several ways. I consider that the differences are of no importance. The fact that accommodation was defective in most of the cases in one group and in only one in the other is fortuitous. The state of the pupil is described differently by the different observers, but I attach much more importance to the points of similarity in the two groups: the presence of abnormal pupillary signs,

mainly unilateral, in healthy young females free from syphilis, some in one group, almost all in the other, also presenting defects in the tendon reflexes.

I feel sure that if the patients described by Foster Moore and by Morgan and Symonds were re-examined it would be found in the first group, where the tonic pupillary reactions were detected, that many of the patients also have loss of reflexes, and in the other group where the reflexes were always affected, that the abnormal pupils already present tonic reactions or that these will be found later if the patients are examined at intervals.

The more carefully I examine these cases the more I am convinced that true iridoplegia is rare. I have a patient in hospital at present whose pupils appear to be fixed to light and on convergence. The patient herself has noticed that they vary in size; sometimes they are quite small. Prolonged exposure to bright diffuse light brings about a definite contraction. The findings on convergence are very instructive: for five seconds or more no movement occurs; then contraction begins and goes on slowly through a wide range; dilatation is still more tardy. On one occasion I counted ten slowly before the contraction on convergence was noticeable.

Nevertheless the pupil in this disorder may be so stiff that at the time of examination no reaction to light or on convergence is obtainable.

Axenfeld, an experienced ophthalmologist with special knowledge of the tonic pupil, saw a young woman at the age of 19 who stated that she had always had unequal pupils; both pupils were then "completely fixed." He examined her again a year later when "a slight contraction occurred on prolonged convergence." Three years later her vision suddenly became defective; at this examination the pupils showed a typical tonic convergence reaction. Accommodation was very slow; after the patient had fixed a near object for thirty seconds, forty seconds elapsed before complete relaxation occurred. The findings were much the same after six and nine years. The knee-jerks and ankle-jerks were absent; the Wassermann reaction in the blood was suspicious on one occasion, negative on another. The signs were attributed, on this evidence, to congenital syphilis.

Reitsch found at a first examination "ophthalmoplegia interna"; four years later the dilated pupil contracted on convergence down to 1·5 mm. in 8 sec. and dilated still more slowly.

One of my patients presented a perfect tonic convergence reaction in

one pupil; in the other, which had recently dilated suddenly, I was unable to obtain any contraction on convergence.

In another, with no history of sudden dilatation, but, like the one just mentioned, with difficulty in accommodating, one pupil was tonic on convergence while the other larger one seemed to be fixed. It may be that my examination was not persistent enough in these cases. Nevertheless they show that in cases certainly belonging to our group the pupils may appear to be inactive on convergence. The cases of Axenfeld and Reitsch tend to confirm the surmise I made in my earlier paper on this subject that the dilated and apparently fixed pupil becomes tonic in the course of time.

The typical tonic pupil then appears to be inactive to light but reacts after a sojourn in a dark room; it contracts slowly on convergence through a wide range and dilates still more slowly. But we must be prepared to encounter many cases of the disorder in which the pupils do not conform strictly to this description. The pupil may contract feebly to light when ordinary methods are used. The reaction to light is often unobtainable by any method; or it may be found in one eye but not in the other when suitable tests are made. The contraction of the pupil may be normal on convergence, dilatation only being delayed. The tonic convergence reaction may be present in one eye while the other pupil is fixed. In unilateral cases the abnormal pupil may be fixed to light and on convergence. The pupil may be fixed at the time the patient is first seen and show tonic reactions later; or a pupil known to be tonic may suddenly dilate and become fixed. Whether such a pupil ultimately becomes tonic again I do not know, but I suspect that it does.

The Relation of the Tonic Reaction to other Abnormal Pupillary Reactions.

In so far as the tonic pupil is or seems to be inactive to light but contracts on convergence it conforms to the prevailing loose definition of the Argyll Robertson pupil. It is for this reason that patients with tonic pupils with and without loss of tendon reflexes are almost invariably thought to be suffering from syphilis of the nervous system.

The true Argyll Robertson pupil, as I have emphasized elsewhere, is an infallible sign of syphilis; its characters, as described by its discoverer, are that it is small, usually bilateral, constant in size, and unaltered by light or shade; it contracts promptly and fully on convergence and dilates again promptly when the effort to converge is relaxed; it dilates

slowly and imperfectly to mydriatics. It thus differs from the tonic pupil in every essential particular and can hardly be confused with it by anyone who is familiar with the characteristic features of both anomalies.

Behr's view is that the tonic reaction differs essentially from the other well-known abnormal reactions: Argyll Robertson pupils, fixed pupils and ophthalmoplegia interna.

The tonic reaction was confined to one side in 80 per cent. of the cases I have seen or analysed; the Argyll Robertson pupil, in my experience, is unilateral in about 5 per cent.; the fixed pupil in less than 10 per cent., and ophthalmoplegia interna in about 20 per cent.

The tonic pupil is almost without exception larger than its normal fellow; the unilateral Argyll Robertson pupil is always the smaller.

If we distinguish between small (under 3 mm.) and large pupils the tonic pupil is never small, whereas the Argyll Robertson pupil is small in 75 per cent., the fixed pupil in 9 per cent., and the pupil of internal ophthalmoplegia in 10 per cent. (Behr).

The tonic pupil varies in size from time to time and may show hippus confined to the affected pupil. It often dilates in the dark and then becomes equal in size with its fellow. This never happens to the Argyll Robertson pupil.

The behaviour of the tonic pupil on subsequent exposure to bright diffuse light is peculiar to it. In other abnormal pupils a slight change may be detected in similar circumstances, but the range of the movement is very narrow and contrasts strongly with the full or even excessive movements of tonic pupils.

The tonic reaction on convergence differs from the contraction on convergence of the Argyll Robertson pupil in that in the latter it is typically prompt and dilatation after the act ceases is also prompt.

The fact that the tonic pupil contracts through a normal or wide range suggests that there is no true paralysis or paresis, but some qualitative change in its mobility. This also applies to accommodation: the movement is slow but not reduced in range; it always corresponds to the age of the patient (Axenfeld). This is essentially different from the findings in ophthalmoplegia interna where the narrow range of movement on accommodation is decisive for diagnosis.

Syphilis is an important factor in the production of other abnormalities of the pupil. Here it plays no part.

This evidence supports Behr's contention that the tonic reaction is distinct from all the other known forms and that it is a manifestation

of a disorder *sui generis*. The fact that the extra-ocular nervous phenomena are unlike anything with which we are familiar also supports the view that we are confronted here by a hitherto unknown kind of perversion of nervous activity.

The Tendon Reflexes.

In the published reports on forty-four patients with tonic pupils, loss of one or more of the tendon reflexes is mentioned in nine; this is either passed over without comment or accepted as further evidence of the presence of syphilis of the nervous system.

All of these cases were described by ophthalmologists; it is almost certain therefore that the proportion with some defect in the reflexes is much higher than these figures indicate. Of nineteen patients with a tonic pupil that I have seen myself thirteen had abnormal reflexes.

Loss of one or both ankle-jerks is most frequent; I have never seen loss of any other jerks with both ankle-jerks still present. Sometimes one or more of the arm-jerks cannot be obtained at a time when the knee-jerks though sluggish can still be obtained on reinforcement.

Asymmetry is not uncommon. I have seen two cases with the knee and ankle jerks absent on one side and still present on the other. In one of these patients the remaining knee-jerk seemed to be abnormally brisk.

In one of Behr's cases the knee and ankle jerks were absent; three years later the ankle-jerks could be obtained on reinforcement. One of Axenfeld's patients was examined "repeatedly" over a period of nine years by expert neurologists; the triceps, knee, and ankle jerks were absent throughout. I suspect that jerks once lost do not return.

One of Oloff's patients had been in hospital five years before when the knee-jerks were present. At the second examination they were absent. The absence of reflexes therefore is probably not congenital.

General Features.

Of my own cases fifteen were females, four males. Including the cases described by others, the figures are forty-five females and eighteen males. The proportion of males thus rises when cases with pupillary abnormalities alone are taken into account. It may be that females are not only more susceptible but also that they are more likely to lose their tendon-jerks.

The age at which the signs appear has not yet been determined. Some patients state that the pupils have "always" been unequal.

This was noticed in one of Foster Moore's patients at the sixth month; at the age of 5 years this patient presented typical tonic reactions.

Most of those who complain of sudden mistiness of vision and dilatation of the pupil are in the twenties and thirties; but this gives no indication of the age at which their pupils became tonic, because, as we have seen, a pupil known to be tonic may dilate suddenly at any time and cause visual symptoms.

Mackay examined Bramwell's case, a healthy unmarried woman, in 1894, and found normal pupils; in 1906 when she was about 38 years of age he found unequal pupils with "no apparent reaction to light in either." This is the only case I have been able to find where an expert has found normal pupils at one examination and tonic reactions at another, and this is not a proven case of our disorder.

My impression is that the abnormal pupillary reaction may appear at any age. The cases of Oloff and Axenfeld, already mentioned, suggest that this is true for loss of reflexes also.

In many cases, perhaps in a large majority the disorder is symptomless throughout life. In a few the onset appears to be sudden; in the course of a game perhaps, some discomfort is felt in and around the eye and vision becomes misty; when the eye is inspected it is found that one pupil is dilated and examination reveals defects in accommodation and in its reactions.

I have never heard of a case with symptoms that could be associated with the loss of reflexes in the lower limb. Repeated careful examinations by myself and by my assistants have failed to reveal any other evidence of disturbance of the functions of the muscles or nervous system in patients with absent reflexes.

There is nothing in the family history of these patients to indicate that they belong to a neuropathic or degenerate stock; nor does anything in the personal history recur with sufficient frequency to deserve mention as a possible ætiological factor. Their general health is remarkably good. They are not nervous; they do not conform to any special physical type.

Relation of the Disorder to Syphilis.

In 1921, when Behr discussed this subject, he had to contend with the fact that most of the writers who preceded him had attributed the tonic pupillary reaction to the effects of syphilis; they based this diagnosis on the ocular signs alone, believing that the tonic pupil was a form of the Argyll Robertson pupil and they made it with still greater

confidence when absence of tendon reflexes seemed to confirm it. Nevertheless, from his study of twenty-one cases in the literature and eight cases of his own, Behr formulated the following cautious conclusion: the presence of pupillotonia alone does not justify the assumption that the patient is suffering from syphilis of the nervous system. Our position now, based on a study of over sixty cases, is much stronger.

The majority of the patients are healthy young females; the ocular signs they present are not observed in syphilitics; in many of them tendon areflexia persists for many years without the addition of any other sign or symptom referable to disease of the nervous system. A patient with evidence that this disorder was present in childhood has lived to the age of 75 without nervous troubles (Foster Moore).

I know of eighteen cases of tonic pupil with absent tendon reflexes in which the blood and cerebrospinal fluid were examined; the results were negative in all. In five more the blood alone was tested, with negative results.

Without making another search throughout all the published reports I cannot give the exact number of the cases of tonic pupil alone in which the blood and cerebrospinal fluid were examined, or the blood only, but tests were made in many cases with negative results in all but one (Barkan's case) in which the reaction in the blood was positive. In this case there was no other evidence of syphilis of the nervous system.

I think the following conclusions may now be drawn with safety: the tonic convergence reaction in pupils only apparently inactive to light is, in all probability, never a manifestation of syphilis of the nervous system. The combination of this sign with absent tendon reflexes and without other signs of organic nervous disease has never been observed in syphilis of the nervous system; it is not one of its manifestations.

Diagnosis.

The diagnosis of this disorder in its complete form presents no difficulty; the combination of the tonic convergence reaction in a pupil apparently inactive to light, with absence of one or more of the tendon-jerks, is pathognomonic.

In the incomplete forms, that is where tonic pupils alone, or "iridoplegia" or "internal ophthalmoplegia," alone or with absent jerks, are found there may be some difficulty.

It must be understood that slowness of movement by itself does not constitute a tonic reaction; that is seen in retinal disease, in traumatic iridoplegia and in many other dissimilar affections of the visual and oculomotor mechanism. The decisive diagnostic features of the true tonic pupil are delay as well as slowness in responding, the inactivity to light which is only apparent, its tendency to retain a new size after the stimulus is removed, and its much slower relaxation compared with the rate of contraction to light, on convergence and, when present, in accommodation.

With regard to cases of "iridoplegia" or "internal ophthalmoplegia" with absent reflexes: the eye signs are almost always unilateral; a history of long standing inequality of the pupils, of recent sudden increase in the size of one of them, perhaps with misty vision, of wide variations in the size of the larger pupil, or the presence of hippus confined to the larger pupil, is decisive. Occasionally tonic reactions in the smaller pupil give the clue. Even if the smaller pupil is normal, or the signs are bilateral, appropriate tests will almost always reveal tonic reactions. To elicit the light reflex it may be necessary to place the patient in a dark room for an hour and then expose the eyes to very bright diffuse light; the light from a pocket torch rarely suffices to start a contraction. To elicit the reaction on convergence persistence may be required on the part of the patient and the examiner; I have seen five and ten seconds elapse before any contraction could be seen. If accommodation is tested in patients with misty vision it will probably be found that the movement though slow is not limited in range. Tonic convergence on accommodation in patients who make no complaint is probably much commoner in this disorder than is recognized at present. Its discovery would clinch the diagnosis, as it is never observed in other conditions.

It may be that tonic reactions would be found in all of these cases if our tests were thorough. I believe, however, that they may be unobtainable in a pupil that has recently increased suddenly in size. If this is so the diagnosis, in patients without changes in the reflexes, may be in doubt for a time; but it can still be made with considerable confidence if the signs are unilateral in a healthy young female otherwise free from signs of organic nervous disease, especially if there is a history of preceding inequality of the pupils.

We have no proof at present that absence of tendon reflexes alone may be a manifestation of this disorder. This diagnosis might be entertained if the signs are of long standing, if other signs and symptoms

of organic nervous disease are missing, and the family history is negative for familial nervous disorders and syphilis.

In the past syphilis of the nervous system was almost always diagnosed or suspected because the tonic convergence reaction in pupils apparently inactive to light was mistaken for the Argyll Robertson phenomenon. So long as the prevailing definition—the pupil reacts on accommodation but not to light—is supposed to define what Argyll Robertson described, the same regrettable mistake will continue to be made. The tonic pupil and the Argyll Robertson pupil have hardly anything in common and should not be confused. Syphilis is usually suspected too in the cases where the pupil appears on superficial examination to be fixed or partially fixed. If efforts to disclose tonic reactions have failed and a careful consideration of all of the features of the case leaves room for doubt, the appropriate tests to exclude syphilis must be made.

Diphtheria can produce ocular symptoms and loss of tendon reflexes. This diagnosis had been suggested in more than one of my cases. It has never been known to cause a tonic reaction on convergence, though its ocular symptoms have been closely studied by many competent observers. The internal ophthalmoplegia of this disease has characters which render it entirely distinct from other forms; there is a true paralysis of accommodation which is almost always isolated and always bilateral; it usually appears about ten weeks after the outset of the disease and complete recovery always occurs in a month or two; it never passes over into tonic accommodation (Axenfeld).

The ocular manifestations of encephalitis lethargica too have been closely studied in recent years; tonic reactions have never been observed. The tonic convergence reaction was well known to ophthalmologists many years before encephalitis lethargica became common. No patient with tonic reactions has ever been known to present any of the recognized early or late symptoms of this disease.

Nature of the Disorder.

The tonic reaction seems to be the expression of a unique kind of perversion of pupillomotor activity. A stimulus is applied; for a time there is no response; then a contraction begins and continues at an ever diminishing rate but through a range in excess of the normal; once begun this contraction may continue after the stimulus is removed; or having reached its maximum it retains it long after the stimulus has ceased to

act; relaxation then proceeds with even greater slowness than contraction.

The curious manner in which stimuli are stored in excess and slowly emitted points to some change in the activity of the cells in the vegetative portion of the oculomotor nucleus. We are driven to the viscera for analogous types of innervation.

The problem raised by the tendon areflexia is one that we have been forced to consider in relation to other disorders of the nervous system.

We are most familiar with this abnormality as a sign of disease of the spinal cord or peripheral nerves, but we encounter it in a number of conditions in which the central nervous system, apart from the vegetative nervous system, is intact.

In dystrophia myotonica and other myopathic atrophies absence of knee and ankle jerks is seen in patients with powerful unwasted lower limb muscles and intact sensibility. The extra-muscular phenomena in dystrophia myotonica point to a disorder of the vegetative nervous nervous system.

In family periodic paralysis the tendon reflexes may be absent for hours or days. In the intervals there are no organic signs. During the cataplectic attacks in narcolepsy the tendon reflexes are completely abolished. In the cases where narcolepsy is symptomatic of encephalitis lethargica, the common association of obesity and the occasional occurrence of disturbances of sugar and water metabolism, vasomotor and heat regulation and the like indicate the region of the brain whose functions are disturbed.

I have seen complete abolition of the tendon reflexes in a patient with myasthenia gravis at a time when there was no weakness in the limbs.

A young woman who was recently under my care at the National Hospital illustrated the close relation of a number of disorders of the vegetative nervous system to which for convenience we attach distinctive labels. She attended first for severe Graves' disease with all the classical signs; on examination she was found to have in addition almost complete external ophthalmoplegia, tonic pupillary reactions and complete abolition of all the tendon reflexes in the upper and lower limbs. The signs were all present while she was still able to attend as an out-patient; power and sensibility in the limbs were then intact. Some weeks later she entered hospital with severe myasthenia gravis from which she died. Apart from the myasthenic symptoms there were no neurological signs; the Wassermann reaction in the blood was negative and the cerebrospinal fluid was normal in every respect.

Most of these diseases present ocular signs. There can be little doubt that they are all related, more or less closely.

Summary.

The tonic pupillary reaction, under a number of different names, has been known to ophthalmologists since 1902.

In some of their cases absence of one or more of the tendon reflexes was noted, but this was misconstrued as further evidence that the ocular signs were due to syphilis.

My conclusions here are based on a study of nineteen patients with tonic pupils, thirteen of them with absent tendon reflexes, that have come under my own observation, and forty-four published cases of tonic pupil, nine with absent tendon reflexes, that have been reported, almost all, in journals of ophthalmology. The cases with tonic pupils and absent reflexes are tabulated.

The disorder manifests itself in complete and incomplete forms. The complete form is characterized by the presence of the tonic convergence reaction in pupils only apparently inactive to light and absence of one or more of the tendon reflexes. The term incomplete forms is used for cases with (*a*) tonic pupillary reactions alone; (*b*) atypical phases of the tonic pupil alone (usually mistaken for iridoplegia or internal ophthalmoplegia); (*c*) atypical pupils with absent tendon reflexes; (*d*) absent tendon reflexes alone.

The tonic pupillary reactions are described in detail and discussed in relation to the Argyll Robertson phenomenon, fixed pupils and internal ophthalmoplegia. The conclusion is reached that the tonic pupil is essentially different from them. The features that distinguish it from the Argyll Robertson pupil are emphasized. The incidence and distribution of tendon areflexia is given and the general features of the disorder are described. The age of onset cannot be determined; females preponderate largely; the cause is unknown. The disorder runs a benign course and rarely causes trouble. Occasionally vision is affected by defective accommodation.

Evidence is adduced to show that the disorder is unrelated to syphilis.

The diagnosis is discussed and reference is made to the necessity that sometimes arises for persistence on the part of the patient and the examiner, lest easily recognizable tonic reactions be missed. Under differential diagnosis, syphilis, the ocular manifestations of diphtheria and encephalitis lethargica are mentioned only to show that they never produce the symptoms found in this disorder.

Other conditions are referred to in which the tendon reflexes are lost temporarily or permanently in the absence of disease of the spinal cord or peripheral nerves.

The conclusion is reached that the symptoms described are the manifestation of a disorder of the vegetative nervous system. They are the expression of a kind of perversion of nervous activity of which at present we can form no conception.

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THE PART PLAYED BY THE SYMPATHETIC SYSTEM AS AN AFFERENT MECHANISM IN THE REGION OF THE TRIGEMINUS.

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FOREWORD BY CHARLES H. FRAZIER, M.D., SC.D.

In the Neurosurgical Clinic of the University Hospital of Philadelphia, because of the abundance of material, we have had a vital interest in the nervus trigeminus. We have in our files 1,832 cases of major trigeminal neuralgia and have performed 711 major operations.

We have been concerned for some time with certain forms of sensation which have been conserved or which have appeared after total or subtotal section of the sensory root. With this in mind, I sought the co-operation of Professor Harry Helson who has devoted much time to the investigation of cutaneous sensation.

This research was inaugurated with an entirely open mind as to the possible results. The examinations of the various forms of sensation were conducted by Professor Helson with the meticulous technique known only to those experienced, as Professor Helson is, in the test for the different forms of cutaneous sensation.

Hours were spent on individual cases and, so far as I know, examinations such as these have never been made, after severance of the sensory root of the trigeminus. Altogether fifteen cases were selected at random for this research.

The product of this research may prove to be of great scientific importance. A number of phenomena quite unexpectedly have been revealed. Their significance I am not prepared to evaluate.

Among other things it was observed: (1) that after a period of years sensitivity to deep pressure increased one hundred-fold; (2) that there developed after one or more years a pronounced improvement in the ability to localize a given point; (3) that there was a response to extremely hot stimulus described by the patient as stinging or burning; (4) and, this seems to me of far-reaching importance, this sensitivity to

extreme heat was entirely lost when in addition to section of the sensory root a thoracic sympathectomy had been performed. May not this be offered as evidence supporting the growing belief that the sympathetic system has an afferent as well as an efferent function? Professor Helson's observations follow.

In spite of numerous observations made upon the regions supplied by the trigeminal nerve after total or subtotal section of the sensory root, many questions still remain unanswered concerning the afferent mechanisms by which certain sensations are mediated after destruction of the one nerve commonly supposed to be responsible for all sensations of the face. There must be afferent mechanisms not only for the paræsthesias that sometimes appear after the radical operation for trigeminal neuralgia, but also for the gradual restitution of certain sensory functions which indubitably occurs. That these are not due to regeneration of the trigeminal tract will be readily admitted by all familiar with the technique of the radical operation, which involves sectioning of the trigeminal root central to the Gasserian ganglion. Nor can the sensations described by certain patients under identical and carefully controlled conditions be dismissed with the assumption that they are purely psychogenic in character. In the hope that some further light might be shed upon the afferent system of the head and face, we decided to make an intensive survey of the sensory capacities, not only of the regions deprived of the trigeminal supply following the radical operation for trigeminal neuralgia, but, for purposes of comparison, of cases deprived both of the trigeminal and sympathetic supply after removal of the first and second thoracic ganglia and the intervening trunk.

To make the investigation as accurate and complete as possible we examined a number of patients at various intervals following operation in order to determine if, and to what extent, sensation remains after deprivation of the trigeminal supply and if there is any restitution in sensory function as time goes on. In our examinations we employed the methods of procedure developed by psychologists and others interested in sensation, for only the most meticulous procedure, utilizing measurements wherever possible, can reveal what sensory functions are present and what changes occur in time. Some fifteen patients in all were examined, but only seven were carefully re-examined a number of times over a period of two years. Our re-examinations showed that improvement in certain sensory functions actually occurs, a fact which

will be stressed in this paper since it throws light upon the possible sources of sensation. All of our subjects were cases in which the second and third divisions of the trigeminal root had been sectioned (sub-total section).

Six classes of sensation were intensively studied: light and deep pressure, sensation of cold, warmth and heat, pain, two-point pressure limen, and the ability to localize a spot within the affected area, also called error of localization. Our discussion of each of these functions will show that the face depends chiefly upon the trigeminal nerve for its afferent supply, but as soon as it is deprived of this source some other nerve, either the facial, the sympathetic, or both, takes over some of the functions formerly mediated by the trigeminal and can be held responsible for the sensations found there. Or may it be through anastomosis with the branches of cervical plexus?

Light and deep pressure.—It is well known that immediately after operation there is no sense of light pressure, but that deep pressures are felt with decreasing sensitivity from the borders of the region toward the malar, infra-orbital and oral regions. Except for isolated spots which may be hyperalgesic, stimulation with human hair or straw fails to elicit any sensation when the stimulus is punctiform. Within a year after operation, however, if the hair or straw is *brushed* or *swept* across the face it will be felt. But properly speaking there is never, at any time after operation, any restitution in the sense of light pressure which seems to be mediated exclusively by the trigeminal nerve and is not taken over by any other nerve. The fact that the stimulus is felt when it is swept across the face will be discussed later.

When we come to *deep pressure* the story is different. Up to a month after operation deep pressures are not felt unless extremely heavy; with a pressure of 4,000 grm. upon a dull stimulus, deep pressure will be appreciated. Within a year sensitivity to this form of stimulation has improved to such an extent that a pressure of as little as 20 grm. in the border regions, and 100 grm. in the regions most affected by the operation, will be felt. After four years 20-40 grm. were felt by two patients throughout the entire area formerly supplied by the second and third divisions of the trigeminal nerve. Here there can be no doubt that restitution of function has occurred since sensitivity to deep pressure has increased at least one hundred-fold.

In 1890 Krause [4] reported that after the radical operation for trigeminal neuralgia he had found in his Case 5 some preservation of pressure sensation in certain areas, but only on deep pressure.

Spiller in 1906 [5] in ignorance of Krause's statement, recorded briefly that in two cases in which the Gasserian ganglion had been removed, he had found that the pressure sensation was preserved, although all other forms of sensation were lost, and was probably the first to attribute the pressure sensation to the nervus facialis. His clinical notes and findings were reported in detail by two of his students, Ivy and Johnson [3], with the definite statement that the seventh nerve conveys fibres of deep or pressure sensibility. Spiller discusses more in detail the preservation of deep pressure sensation after removal of the Gasserian ganglion in his paper on "Tumor of the Gasserian Ganglion," published in 1908.

Temperature.—At all times after the operation temperatures between 15° and 45° C. fail to evoke sensations of cold, warmth or heat. The medium range of temperatures goes when the sensory root is cut, and never returns. However, if an extremely hot stimulus, one between 60° and 75° C., be applied to the malar or oral regions, most patients will report a stinging or pricking sensation. They never used the word "hot" if it were carefully concealed from them that the steel cylinder had been heated. One paradoxical result deserves mention since it was verified on two patients independently, and shows that the new nerve responding to this form of stimulation has not learned its lesson well, so to speak; these subjects reported that a stimulus of 55° C. (ordinarily hot) was cold in the malar region, whereas stimuli normally giving cold failed to be reported as such when applied. To check a suspicion that the sympathetic fibres might be responsible for the responses to extremely hot stimuli, we tested three patients upon whom a thoracic sympathectomy had been performed as well as the radical operation, and we found that they failed to get anything but neutral pressure from the hot cylinders throughout the whole distribution of the trigeminal nerve. One could sear the skin of these latter subjects without getting any response except pressure, while the other patients in whom the sympathetic was not divided reacted very violently if the cylinders were kept on the face more than a few seconds. One perhaps is not surprised that intense heat is described as a stinging or pricking sensation, whereas cold is not felt at all because of the very close association of heat and pain sensations, as seen especially in causalgia. These facts argue for sympathetic participation in some of the sensory functions of the face, at least after the trigeminal supply is gone. No sensations of cold have ever been reported to us even with the application of ice to the operated region, although many patients

report a dislike of cold water or draughts on the affected side of the face.

Pain.—Here we find little or no sensitivity either immediately or as long as six years after operation. As a stimulus we used a needle with 30 grm. pressure which elicits a report of pain on the normal side. This is felt merely as a dull, blunt pressure. We therefore might conclude that normally the trigeminal nerve alone mediates the pain sense and this function is not taken over by any other nerve. But there are a number of phenomena which seem to show that there is some pain supply in the face after the trigeminal nerve is gone. Some patients complain of spontaneous pains within the operated region, usually in isolated spots. If these spots are touched rather lightly they over-react as if they were hyperalgesic. At the very time that patients complain of spontaneous pains stimulation of the regions concerned often fails to evoke anything more. This fact may be due to the relatively light stimulation which does not penetrate to the deeper-lying tissues and nerves. It must be remembered that the reactions to the extremely hot stimuli occurred only after sufficient time was given to penetrate below the surface. Our inability to evoke pain in the trigeminal region with the 30-grm. needle may be due to the fact that we have not reached the deeper-lying mechanisms possibly responsible for paræsthesias.

TABLE I.—IMPROVEMENT IN ABILITY TO LOCALIZE A SPOT TOUCHED WITHIN THE TRIGEMINAL DISTRIBUTION AFFECTED BY OPERATION.

Patient	Time since operation	Error of localization	
		Operated side	Normal side
D.	6 years	8·57 ± 5·39 mm.	4·09 ± 2.20 mm.
H.	2 months	10·12 ± 5·57	5·76 ± 4·59
	11 months	8·06 ± 5·10	
M.	5 months	14·17 ± 11·90	4·81 ± 2·48
	13 months	12·95 ± 9·50	
Pe.	3 years 1 month	13·30 ± 6·98	3·78 ± 2·17
	4 years 3 months	12·37 ± 9·25	
Po.	5 months	11·53 ± 8·34	4·66 ± 3·38
	12 months	10·82 ± 4·96	
V.	3 weeks	18·50 ± 11·10	4·50 ± 2·35
	9 months	9·09 ± 5·50	
Y.	10 months	11·19 ± 6·26	4·42 ± 2·27

Localization.—We find the most pronounced improvement in the ability to localize a spot touched within the operated area. This follows from, and is a check upon, our earlier finding that sensitivity to deep pressure improves remarkably. In Table I will be found the average error of localization with its standard deviation at various intervals since

operation for the operated side of the face and for the normal side. The most striking case is that of patient V, who shows an error of localization of 18·50 mm. three weeks after operation, as compared with an error of 9·09 mm. nine months after operation. It looks as if some other nerve is "learning" the function formerly mediated by the trigeminus. The table shows that improvement occurs rapidly during the first year after operation and then proceeds more slowly for a year or two, after which a stationary state is reached wherein ability to localize is still far from normal, but definitely better than immediately after operation. The change from absolute inability to localize a spot within the trigeminal region to an error only twice as great as the normal error is most striking indeed. Whether we are dealing here with vicarious functioning of the seventh nerve for the fifth or sympathetic involvement, we shall discuss later.

Two-point limen.—By this is meant the ability to discriminate two points as two. This function, an epicritic function according to Head and his co-workers, is irretrievably lost with the trigeminal because two points of the æsthesiometer, no matter how far apart, applied within the trigeminal distribution are felt as one, if felt at all. When asked where the one point is felt, the patient sometimes chooses a spot between the two spots actually stimulated or one or the other of the spots touched.

Except for light pressure, pain (?), medium range of temperatures and two-point limen, there certainly appears to be restitution of certain sensory functions in the regions formerly served by the trigeminal nerve. The retraction of the border regions, improvement in ability to sense deep pressures, to localize spots, to feel extremely hot stimuli, and a generally heightened sensitivity in the region force us to assume that peripheral neural mechanisms are present to mediate these. We can say either that the facial nerve alone is responsible, since it is known to carry some sensory fibres; that the sympathetic nerve also has sensory functions which appear when the trigeminus is gone; that an anastomosis has been established with the cervical plexus; or that all three nerves are playing a part in the new sensory picture we have delineated after trigeminal resection.

It is easy to assert that the facial nerve is alone responsible for all of these sensory functions, except for the fact that in the cases where the sympathetic supply was gone as well as the trigeminal but the facial remained, there was no response to extremely hot stimuli anywhere in the region. Furthermore, the fact is well known that

temperature reactions are closely associated with the contractions of muscles supplying the veins and arteries, a fact which the "temperature spot" theories of temperature sensations have tended to neglect but which is most important in showing their relations to the sympathetic system. The intense dislike of, and shrinking from, cold air and water exhibited by many patients after the radical operation appears very much like a total reaction characteristic of sympathetic functioning, for it is only when the whole face is affected by cold that the disagreeable feelings are reported, since the application of ice in a punctiform manner failed to elicit unpleasantness. The fact noted above that in order for a light touch to be felt the hair or straw must be swept across the skin, argues for some afferent mechanism whose functions are more diffuse and totalized than usually associated with peripheral cutaneous nerves. We are therefore forced to conclude that we have here *bona fide* evidence for the rapidly growing belief that the sympathetic and parasympathetic systems have afferent as well as efferent functions.

It is hardly necessary to point out the rich supply of sympathetic fibres to the face—fibres from the internal carotid plexus to the Gasserian ganglion, from the ciliary, sphenopalatine, otitic, and submaxillary ganglia. As Frazier [2] has previously said: "These rich sympathetic connections may not be without their significance. Operations upon the cervical sympathetic ganglia have been practised for many years for the purpose of relieving pain, as in trigeminal neuralgia and migraine . . . when one stimulates electrically the cervical sympathetic ganglion or the periarterial sympathetic plexus of the common carotid artery . . . the patient frequently complains of pain within the zone of the trigeminal distribution."

By means of this assumption, that the sympathetic has an afferent as well as an efferent function, we find ourselves in a better position to understand the sensations which remain and develop after section of the sensory root of the trigeminus. Our findings support the conclusions reached by Foerster, Altenburger and Kroll [1] that the sympathetic plays a sensory role in every part of the body, and that to de-afferent a region completely the sympathetic supply must be taken away as well as the peripheral nerve supply commonly supposed to mediate cutaneous sensations. Owing to the numerous sources of sympathetic supply, it is most difficult to be sure from purely operative procedures alone when a complete sympathectomy has been achieved. Our investigations of the sensations in the face after loss of both the trigeminal and sympathetic supplies shows a different state of affairs from that seen when only the

trigeminal supply alone is lost. The sensory functions of the sympathetic appear (or may even develop) when the masking effect of the trigeminal disappears, because we certainly find further loss in sensation when, in addition, the sympathetic supply is taken away. The absolute zero of cutaneous sensitivity can be reached not merely through resection of the peripheral nerve supply (trigeminal and intermedius) but requires deletion of the sympathetic supply as well. We may here have the key to that class of neuralgias called "atypical" from the point of view of traditional theories of nerve functioning.

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ON SUPRASELLAR CHOLESTEATOMAS.[1]

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Stockholm.

THE chiasmal syndrome and its variations are now fairly well known, thanks mainly to the work of Harvey Cushing. The more common types of suprasellar lesions may thus be readily recognized before operation in the majority of cases. Diagnostic errors are, however, easily committed when the lesion is of some more unusual histological type, or when the nature or extension of the pathological changes is variable, as in cisternal arachnoiditis. That cholesteatomata, when arising in the suprasellar region, may occasion a peculiar variation of the chiasmal syndrome, which seems to be sufficiently characteristic to enable a correct pre-operative diagnosis, is shown by the following two cases.

Case 1.—G. M., female, aged 19, Surgical Clinic, Serafimerhospital No. 138/31.

Apart from a birth palsy (plexus injury) of the right arm the patient had always been in good health until August, 1925, when she began to have double vision. This persisted for a month and then disappeared. At the same time she noticed that she could not see as well as previously. Otherwise there were no symptoms, no headache or vomiting, and after the double vision had disappeared the patient felt perfectly well apart from her declining vision. In May, 1928, she consulted an eye specialist because she could not see well enough to read without glasses. At this examination it was found that she was blind in the right eye, and that vision in the left eye was reduced to 0·4. The fundi showed a primary optic atrophy of an exteme degree. She was given antisyphilitic treatment for two years. During this time vision in the left eye remained practically stationary, but there was a slowly progressing constriction of the visual field from the temporal side. She was sent here in July, 1930, by Dr. Dymling, with the diagnosis of suprasellar tumour, but when she was advised to enter the hospital for observation she returned home and did not appear until January 23, 1931.

When the patient entered the hospital her only complaint was that she could not see well and she thought that a further decrease in visual acuity had

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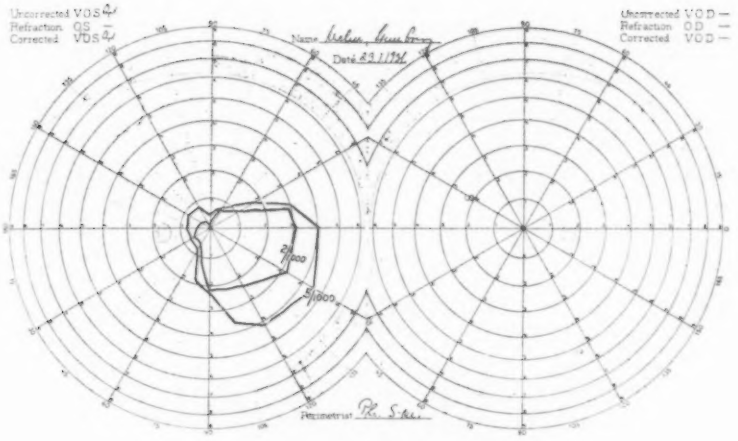

FIG. 1 (*Case* 1).—Visual field before operation.

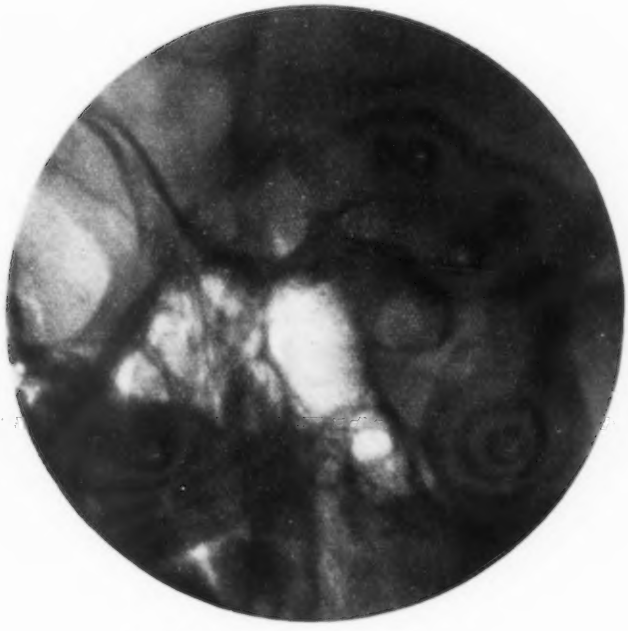

FIG. 2 (*Case* 1).—Right optic foramen.

taken place since July, 1930, when it had been found to be 0·4 in the left eye. She was a slender but normally developed girl of 19. Menstruation started at the age of 13, and had been normal ever since. Her skin was fine in texture but within perfectly normal limits. Secondary sex characteristics were normally developed. Hair was normal in texture and distribution. Her basal metabolism was + 34.

FIG. 3 (*Case* 1).—The sulcus chiasmatis of the sphenoid bone is very much enlarged and is about three times as wide as normal. The anterior clinoids also show some pressure absorption.

Examination of the eyes showed both pupils to be wide but reacting to light, though very sluggishly in the right eye. The right eye was blind and visual acuity in the left eye was reduced to 0·1. Examination of the visual field showed that only the lower nasal quadrant was left (fig. 1). The macular region was spared. The fundi showed a primary optic atrophy of an extreme degree. Both discs were chalky white with sharp margins. The vessels seemed to be normal.

Neurological examination otherwise was entirely negative. Roentgen examination of the head (Dr. Lysholm) showed that both optic foramina were wider than normal and measured about 6 to 7 mm. in diameter (fig. 2). The sulcus chiasmatis of the sphenoid bone (fig. 3) was very much enlarged. The sellar region otherwise was essentially normal as well as the rest of the cranium. No suprasellar calcifications could be detected although such changes naturally were searched for with particular care, and no bony prominence in the region of the tuberculum sellæ suggestive of a meningioma could be seen.

That a compression of the optic chiasma was present in this case could hardly be doubted in view of the primary optic atrophy, the field defects and the slowly progressive character of the lesion. Since, however, the clinical picture did not fit in with any of the known variations of the chiasmal syndrome, the nature of the lesion was difficult to determine. In view of the age of the patient, a craniopharyngioma seemed to be the tumour most likely to be expected, even though suprasellar calcifications were absent. The complete absence of disturbances of pituitary function was difficult to reconcile with this diagnosis, since some degree of pituitary insufficiency is almost always present in cases where the optic atrophy has reached a high degree, and is usually very marked in cases of this type. It is also very unusual to see a craniopharyngioma without even a trace of deformity or pressure absorption of the posterior clinoids, and in most cases where pressure on the optic chiasma has been sufficiently marked to cause pallor of the discs to an appreciable degree the roentgenological changes of the sella are outspoken. The unusual widening of the optic foramina naturally focused attention on the possibility of a glioma of the chiasma, but these tumours sooner or later come to involve the floor of the third ventricle, and in the absence of any evidence of extension of the lesion to this region, in spite of the long duration of the malady, a glioma of the chiasma was thought to be a very remote possibility. A suprasellar adenoma or a meningioma from the tuberculum sellæ were the favoured diagnostic possibilities, but in both cases the age of the patient was considered to be an argument of considerable weight against this diagnosis. The widening of the optic foramina was difficult to explain as caused by any of these lesions, but we were then inclined to discount this finding and regard it as accidental. The widening of the sulcus chiasmatis might have been caused by a suprasellar meningioma, which therefore was regarded as perhaps the lesion most likely to be found.

Operation, January 29, 1931. Under local anæsthesia a right-sided transfrontal flap was turned down and the chiasmal region explored. After the

dura had been opened along the lesser wing of the sphenoid neither optic nerve could be seen. The space above and anteriorly to the optic nerves was occupied by a mass of a pale whitish-yellow colour which completely concealed the chiasma and both optic nerves. After the mass had been incised the soft cheese-like contents of a typical cholesteatoma began to extrude. The cholesteatomatous masses were included within a thin capsule which on the inside had a velvet-like appearance with thin layers of glistening pearly matter

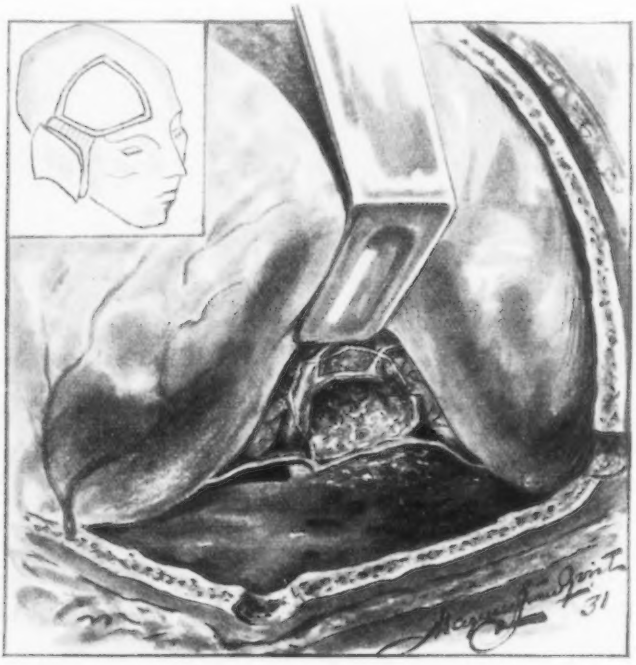

FIG. 4 (*Case* 1).—Sketch of the field of operation. The contents of the tumour have been cleared out and the arteries on the base of the brain can be seen through the thin capsule.

adhering to it in places. After most of the cholesteatomatous masses had been cleared away with a suction apparatus all the big vessels on the base of the brain could be seen through the thin capsule (fig. 4). As is usually seen in cholesteatomas the capsule insinuated itself into every cleft and crevice of the neighbourhood in the form of multiple spurious herniations filled with cholesteatomatous matter. The optic nerves could not be seen. They were probably flattened out and plastered to the underside of the capsule and it was not thought wise to search much for them as they might easily be damaged in

the procedure, as we learned in the following case where a more radical procedure was adopted. For the same reason, and because the capsule was found to be somewhat adherent to the blood-vessels, no attempt was made to remove the capsule, of which only a slip was taken for examination. The cavity, which was approximately the size of a golf-ball, was filled with salt solution and the wound closed without drainage.

Microscopical examination (Professor Bergstrand) of the tissues removed at operation showed the tumour to be a typical cholesteatoma. The healing of the wound was perfect and convalescence undisturbed except for a mild transitory polyuria, which however never exceeded 2,000 c.c. per twenty-four hours. The patient was discharged on February 18, with visual acuity and field practically unchanged. In June, 1931, she reported herself to be in excellent health and her vision had improved to 0·3, although the visual field was unchanged.

The second case came under observation within a few days of the first, which naturally greatly facilitated a correct pre-operative diagnosis.

Case 2.—E. E., a female, aged 27. Surgical Clinic, Serafimerhospital, No. 128/31.

Since the age of 9 the patient had suffered from headache coming on in attacks usually once or twice a week. The headache was at first localized over the right eye and in the right temple, radiating towards the right occipital

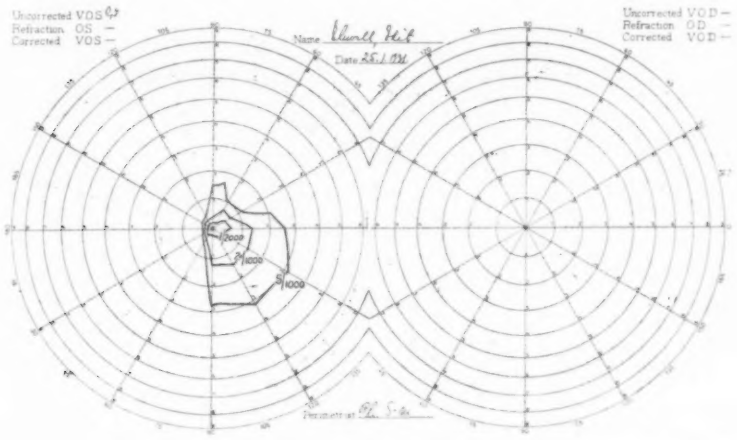

FIG. 5 (*Case* 2).—Visual field before operation.

region. After the right eye had become blind five years previously the headache had been less severe, had not occurred so often and had been more localized to the corresponding regions on the left side. The headache had never been very

severe and could always be entirely relieved by aspirin. There had never been any vomiting. In 1926 the patient noticed that she was almost blind in the right eye, and an eye specialist whom she consulted at that time found that vision in the right eye was reduced to light perception in the nasal part of the field while the left eye was normal. A year later she was completely blind in the right eye. In September, 1930, the patient noticed a decrease of visual

FIG. 6 (*Case* 2).—Enlargement of the sulcus chiasmatis less marked than in the preceding case. Marked pressure absorption of the right anterior clinoid process.

acuity in the temporal field of the left eye which progressed so that after a few months this part of the field was completely blind. She then consulted Dr. Raeder in Oslo, who, on January 21, 1931, referred her to me with the diagnosis of suprasellar tumour.

The patient was a normally developed woman who had always menstruated regularly. The skin was normal in texture. Distribution of hairs was also normal. The basal metabolism was + 4 per cent.

There was a slight convergent strabismus of the right eye, otherwise movements of the eyes were normal. The right pupil did not react to light. The left pupil reacted normally to light and accommodation. The right disc was chalky white with sharp margins and narrow arteries. This eye was completely blind. In the left eye vision was 0·9. The disc was definitely pale, especially in its temporal part, and the arteries narrow. Examination of the left visual field showed a result which was identical with the one obtained in Case 1, i.e., integrity of the macula and of the lower nasal quadrant. However, with the smaller test objects even this quadrant showed a considerable degree of constriction (fig. 5).

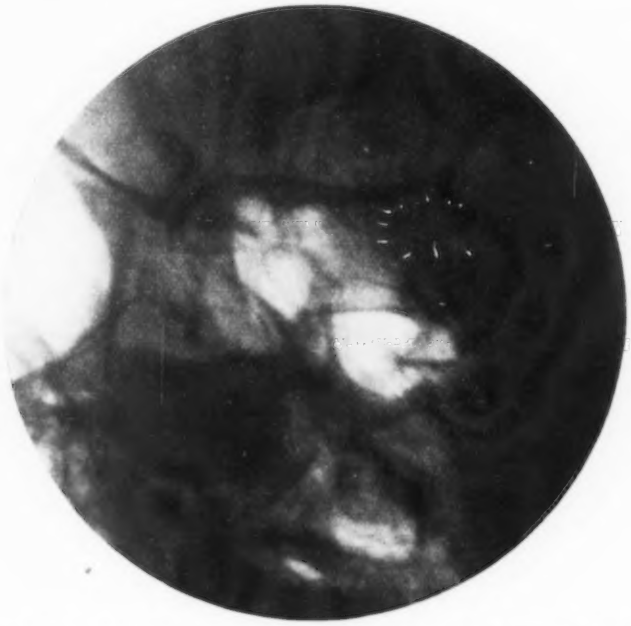

FIG. 7 (*Case* 2).—Right optic foramen very much enlarged and of irregular form with pressure absorption of its margins.

Neurological examination was otherwise completely negative. Roentgenological examination of the head (Dr. Lysholm) disclosed a condition very similar to that in the preceding case, though somewhat more pronounced. The right anterior clinoid process showed a thinning of its central part, merging with a definite erosion of the bone on the mesial and anterior aspect of the process (fig. 6). The right optic foramen was much larger than the left (fig. 7). Otherwise the sella and the rest of the skull were essentially normal, though there was perhaps some slight convolutional atrophy.

Both with regard to history and clinical findings, this case was almost an exact replica of the first, and a pre-operative diagnosis of suprasellar cholesteatoma did not seem to involve much chance of error.

Operation I, February 2, 1931. A right transfrontal flap was turned down under local anæsthesia. The operative findings were exactly similar to those in the preceding case. After the capsule had been incised and the cholesteatomatous masses evacuated one saw the same picture of a thin velvet-like membrane covering the base of the brain and the big vessels. When these were touched with the suction apparatus in the process of cleaning out the contents the patient complained of severe pain in the head. An attempt was then made to identify the optic nerves, which of course was a necessary preliminary to any attempt to remove the capsule. After some search the right optic nerve was identified as a thin greyish strand entirely surrounded by cholesteatomatous masses which seemed to have grown all around it. The left optic nerve could not be seen and further attempts to expose it or to remove the capsule were abandoned for fear of injury to the nerve. As events proved this must nevertheless have been inflicted. Probably the left nerve was, like the right one, completely surrounded by the cholesteatomatous masses and must have been injured or torn during the attempt to expose it, or during the process of cleaning out the contents of the tumour. Only a fragment of the capsule was removed for examination. The cavity, which was of the same size as in the preceding case, was filled with salt solution and the wound closed without drainage.

Microscopical examination (Professor Bergstrand) of the removed part of the capsule showed the tumour to be a typical cholesteatoma.

When vision was examined immediately after operation it was found that the patient was blind. She claimed to have light perception but could not count fingers. As later examinations showed her to be completely blind it is probable that her light perception was imaginary.

Her convalescence was uneventful except for occasional headaches and an unusually slow pulse. The wound healed without reaction and she was discharged on February 25.

A few days later she re-entered the hospital after having had very severe headaches for a few days and high temperature. On examination she was found to have a temperature of between 39° to 40° C., and complained of very severe headache. The flap was not elevated and it was somewhat difficult to explain her condition as there was no sign of wound infection. As long periods of hyperpyrexia and increased intracranial pressure are sometimes seen after operation for cholesteatoma, it was thought that a reaction of this type had occurred. Her pressure symptoms seemed to be so urgent that re-elevation of the flap was indicated.

Operation II, March 3, 1931. Under local anæsthesia the old flap was again elevated. The dura was exceedingly tense. After the frontal lobe had been elevated it was found that the opening in the capsule was closed by

adhesions and when these were separated a large amonnt of thick greyish-yellow pus escaped. Immediate smears showed no micro-organisms. Cultures were taken but these proved to be negative. The cavity was rinsed out with salt solution and the wound closed without drainage.

The case obviously was one of aseptic suppuration caused by the desintegration of cholesteatomatous matter which had been left in the cavity. Similar reactions do not seem very uncommon after operations for cholesteatomas. Critchley and Ferguson [1] mention the occurrence of post-operative febrile reactions in some of their cases. Several years ago I had a case of cholesteatoma in the lateral ventricle where removal of the tumour was followed by a period of hyperpyrexia of several weeks duration, with increased intracranial pressure and turbid, though sterile, fluid in the ventricle from where the tumour had been removed. In another case I observed a fatal aseptic meningitis from spontaneous perforation of a fourth ventricle cholesteatoma. In the present case, wound healing occurred without reaction and the patient was discharged on April 16. Her health has since remained good, but she is completely blind.

The clinical features of the two cases presented above are almost identical. In both cases a chiasmal syndrome of a type unusual for the age of the patients was found. Although suprasellar cholesteatomas, of course, may cause other variations of the chiasmal syndrome, the striking similarity of the clinical features in the two cases just described seem to warrant the conclusion that when the following symptoms are present a diagnosis of suprasellar cholesteatoma may be ventured upon with reasonable certainty :—

(1) A very slowly progressive primary optic atrophy with bitemporal hemianopia occurring in a young person.

(2) An essentially normal sella turcica, but with widening of one or both optic foramina and pressure absorption of one or both anterior clinoids and of the sulcus chiasmatis of the sphenoid bone.

(3) Complete absence of signs of pituitary insufficiency.

The syndrome of suprasellar cholesteatomas, therefore, is in many respects very like the one caused by meningiomas of the tuberculum sellæ, but differs from this syndrome in that it occurs at an age when meningiomas are rare. Furthermore, widening of the optic foramina does not occur with meningiomas, and the widening of the sulcus chiasmatis probably very rarely attains a degree comparable with that observed in Case 1. In the stage when the optic atrophy is as advanced, as in the cases cited above, some degree of pituitary insufficiency is to be expected in the case of a meningioma.

The variations of the chiasmal syndrome caused by different tumours depends upon the size and exact localization of the growth, the age of the patient and the consistency of the tumour.

The cholesteatomas differ from other tumours in this region in several of the above-mentioned respects. They are congenital tumours and therefore symptoms are likely to occur at an early age. Among Critchley and Ferguson's [1] cases the average age of the patients was 37 years, although among their eight cases the average age of the patients was much influenced by the unusual fact that one patient was 73 years old when symptoms first occurred. In my own experience of five cholesteatomas none of the patients was above 32 years when symptoms occurred and the average age was 27. The cholesteatomas are very slowly growing tumours and in the suprasellar region the onset of symptoms is likely to be very gradual. Probably no other tumour in the suprasellar region except the craniopharyngioma is of such a slow growth as the cholesteatoma. The consistency of cholesteatomas is softer than that of any other tumour of the suprasellar region, excepting possibly the adenomas, but even here the more rapid growth of this tumour usually causes a greater degree of tension within the capsule and consequently gives the growth a firmer consistency. Occasionally the craniopharyngioma has a thin soft capsule, though rarely of the same degree as the cholesteatoma, but the fluid within the capsule is usually under considerable tension, which gives the tumour a comparatively firm consistency. It is easy to understand that the surrounding structures easily adapt themselves to the slowly growing cholesteatomatous mass enclosed under little or no tension within its soft capsule, and that in this particular situation the optic nerves are the only structure which cannot evade pressure from the expanding growth. As long as the cerebrospinal fluid pathway is not occluded the intracranial pressure need not be affected. Absorption of bone therefore does not occur except where the cranium is immediately adjacent to the tumour. Thus in cholesteatomas of the cerebral convexity pressure absorption, as shown by Cushing [2] and by Schüller [3], is limited to the bone immediately underlying the tumour and is usually so sharply limited to this part that a diagnosis of the nature of the growth can be made from the appearance of the absorption of bone alone. Probably the sellar diaphragm effectively protects the pituitary body from pressure of the overlying soft tumour, which explains the absence of pituitary manifestations. The blood supply of the surrounding part of the brain is not interfered with, since the arteries do not become compressed but instead

indent the soft tumour. The widening of the optic foramina is explained by the tendency of cholesteatomas to crowd their way into every cleft and crevice of the neighbourhood. In Case 2 where the right optic nerve was identified it was accompanied into the optic foramen by a projection of the tumour.

The peculiar variation of the chiasmal syndrome observed in the two cases described above can therefore be regarded as determined by the characteristic features of the tumour with regard to age of onset of symptoms, rate of growth and consistency. This leads me to conclude that we are dealing, not with a merely accidental resemblance of symptoms in two cases, but that a similar syndrome may be expected in most cases of a tumour of this kind in this situation. Naturally, variations may occur when the tumour happens to be more laterally or posteriorly placed in relation to the chiasma, but even so the principal features of the syndrome should be preserved although the field defects may assume a different type.

With regard to the treatment of these lesions my experience in Case 2 leads me to advise against too much searching for the optic nerves and against any attempt to remove the capsule except in cases where the anatomical relations of the chiasma and other important structures are perfectly clear. In every case of cholesteatoma which has come under my observation the capsule has had intimate relations with a number of large blood-vessels and is apt to have so many herniations into clefts and crevices, where the anatomical relations to neighbouring structures are not clear, that it appears that an attempt to remove the capsule is rarely justified. Nor does the very slow growth of these tumours encourage any hazardous attempts to remove the capsule. In my experience the mere clearing out of the contents of the tumour, leaving the capsule intact, as can be done with very little risk, has been followed by excellent results. Two cases operated on according to this method are living and well 6 and 5 years after operation. A conservative attitude towards these lesions therefore seems to be the wisest policy and I would rather take the chance of a second operation some years later than risk life or serious disability of the patient in an attempt radically to remove the capsule. A measure which may possibly be contemplated in cases where the growth has sent a projection into one or both optic foramina is to remove the dorsal margin of the optic foramen in order to relieve the optic nerve from pressure within the foramen. This manœuvre might also facilitate the identification of the optic nerves.

SUMMARY.

Two cases of suprasellar cholesteatoma are described. The following variation of the chiasmal syndrome may probably be regarded as typical of suprasellar cholesteatomas:—

(1) A very slowly progressing primary optic atrophy with bitemporal hæmianopsia occurring in a young person.

(2) A sella turcica essentially normal, but with widening of the optic foramina and the sulcus chiasmatis of the sphenoid bone.

(3) Complete absence of pituitary manifestations.

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Notices of Recent Publications.

The Selected Writings of John Hughlings Jackson. Vol. II. "Evolution and Dissolution of the Nervous System—Speech—Various Papers, Addresses and Lectures." Edited by James Taylor, with the assistance of Gordon Holmes and F. M. R. Walshe. London: Hodder and Stoughton. 1932. Pp. 500. Price 25s.

In the opening paragraph of the paper with which this volume of his writings begins, Hughlings Jackson quotes from Herbert Spencer as follows: "Every science begins by accumulating observations, and presently generalizes these empirically; but only when it reaches the stage at which its empirical generalizations are included in a rational generalization does it become developed science."

The quotation is a singularly appropriate introduction to a volume which, in fact, contains Jackson's "rational generalization" of the numerous clinical observations contained in his writings. This generalization is expressed in his statement of the evolution and dissolution of function in the nervous system. Throughout his writings on epileptiform convulsions, on paralyses and on disturbances of the speech we see him marshalling the facts of observation until his "rational generalization" emerges inevitably from them. It is in his Croonian Lectures of 1884 that his views are perhaps most clearly and concisely expressed, and it is here that he most brilliantly shows the essential modernity of his outlook.

In that striking work, "Science and the Modern World," Professor Whitehead speaks of the characteristic attitude of the modern mind resulting from the growth of science, and he describes this attitude in terms that may fittingly be applied to the thought of Hughlings Jackson. He says: "This new tinge to modern minds is a vehement and passionate interest in the relation of general principles to irreducible and stubborn facts. All the world over and at all times there have been practical men, absorbed in 'irreducible and stubborn facts'; all the world over and at all times there have been men of philosophic temperament who have been absorbed in the weaving of general principles. It is this union of passionate interest in the detailed facts with equal devotion to abstract generalization which forms the novelty in our present society. . . . This balance of the mind has now become part of the tradition which infects cultivated thought. It is the salt which keeps life sweet."

In no medical writings of our time is this balance of mind so strikingly exhibited, and it is in his combination of acute clinical observer and penetrating discoverer of general principles that Jackson stands out above all other masters in the history of neurology.

While it is probable that there is no observed disorder of nervous function

not comprehended within the scope of his conception of evolution and dissolution of function, it cannot be denied that the task of assessing the place within his scheme of some newly observed phenomenon of disordered function demands from the student of neurology some tincture of the power of abstract thought so richly displayed by Jackson. It is scarcely surprising, therefore, that not all attempts in this direction have been conspicuously successful. The identification of the phenomena of release and their differentiation from those of defect may be relatively simple in the case of some high level dissolution ; such, for example, as we see in a case of residual hemiplegia. It is examples of what Jackson spoke of as " local dissolution " at lower levels that present the greatest difficulties of analysis. The phenomena of cerebellar ataxy provide a striking case in point. Here the disorder of motor function is the algebraical sum of the activities of all the surviving components of the nervous motor mechanisms, and the detection and analysis of the negative, or defect, elements in the clinical picture have proved a task of almost insuperable difficulty. Yet no serious student will deny that within the limits of Jackson's hypothesis an adequate analysis is to be found.

His views upon the evolution of function in the nervous system should also act as a wholesome corrective of much loose thinking current upon this subject. Jackson is primarily concerned with what he terms " internal evolution " of function within the higher levels of the individual nervous system, and his writings contain no facile speculating in the realms of phylogenesis, such as is too common in modern neurological theorizing. Founded, as all his generalizations are upon the solid basis of accurate clinical observation, it is clear that speculations of this order could make no appeal to him.

In some measure, possibly, the undoubted complexity of much of Jackson's writing has stood in the way of a more extended and successful application of his views, but a more important factor is probably the limited capacity for generalization and for abstract thought displayed by some even of the most competent clinical observers. Some factor of this order has led a recent writer to declare that hitherto the application of Jackson's teaching has been fruitless in the interpretation of clinically observed phenomena, and it is easy to find illustrations in the literature that may seem to lend colour to this view.

Nevertheless, we may confidently assert that wherever the laws governing the dissolution or function, as formulated by Jackson, may seem to fail us in interpreting the phenomena of disease, the failure lies not in any lack of validity of these laws, but in a lack of understanding of them.

In referring to the difficulty inherent in the study of much of Jackson's writing, it must of course be borne in mind that in breaking new ground in thought and in formulating new conceptions, the pioneer labours under handicaps which are absent from the treading of familiar paths of thought. Human speech is not a perfect instrument, and Jackson had at call neither a generally accepted neurological terminology to lend brevity to his exposition, nor a developed science of physiology to lend him aid. Yet if his lack of a scientific nomenclature sometimes renders his writing lengthy and not easy

to follow, it has at least the merit that with due study any intelligent student may follow his thought without needing that glossary of terms that has become an indispensable item in the equipment of the reader of much modern writing on neurological subjects. Complex as his phraseology is, Jackson found the English language adequate to all he had to express. His pages are not littered with tags from foreign tongues, nor do they carry the dubious adornment of innumerable and superfluous new-coined words to express what simple English words could as tersely and clearly convey.

The full fruit of Jackson's teaching will be long in the gathering, but in placing these two volumes before the present generation of neurologists Dr. Taylor has brought the harvest nearer and has, we may hope, made its promise as bountiful as Jackson could himself have wished. But those also of an older generation who had the privilege of being Jackson's pupils owe to the editor of these volumes a debt of gratitude for this renewal of the inspiration of Jackson's teaching and for the recollections of this most modest and charming of great men which the re-reading of his writings must bring to them.

Lehrbuch der Nervenkrankheiten. Von R. BING. 4te Aufl. S. 570. Berlin: Urban und Schwarzenberg. 1932. Price 25 M.

The fourth edition of this well-known textbook has been brought up to date and thoroughly revised, but its scope and plan remain unaltered. It is intended for students, and symptoms, therefore, rather than anatomical lesions, determine the arrangement of its subject matter. This has led in places to an unsatisfactory arrangement of the subject; for instance, the dyskenesias, that is all forms of involuntary movement from fibrillation to chorea, paralysis agitans and myotonia, are grouped together in two chapters immediately after those devoted to disease of the peripheral nerves, so that the student meets them before he has learned the more essential features of disorder of the nervous mechanisms concerned in movement.

The pathological aspects of disease are in some instances hardly adequately described or illustrated, and to the student at least the book would have been more useful if more space had been allotted to discussions on the nature and significance of symptoms and signs as evidences of disturbances of functions. The descriptions of the clinical features and of the points on which diagnosis can be based are excellent. A short bibliography has been provided and there is a useful index.

Anatomie élémentaire des Centres nerveux et du Sympathique. Par P. GILIS. 2me Édition. Paris: Masson et Cie. 1932. Pp. 234. Price 24 fr.

The second edition of the late Professor Gilis' small textbook on the anatomy of the nervous system has been prepared for the press by Dr. Euzière, who has found it necessary to make few alterations.

The book was originally planned as an introduction to the study of the

vegetative nervous system, the importance of which in every branch of medicine has been, in the author's opinion, not fully recognized. But he found that it was not possible to describe properly the sympathetic apart from the rest of the nervous system, and therefore devoted the first half of the book to a study of the anatomy of the central nervous system, or, as he calls it, "the system of relation."

Both sections are concisely written and well illustrated by diagrams; the more usually accepted views are followed, and within its scope there are few statements to which exception can be taken. It is consequently suitable for students and for those who desire acquaintance with an outline of the plan and the chief anatomical details of both nervous systems.

Les Agents physiques dans le Traitement des Maladies nerveuses. Par H. SCHAEFFER et E. BIANCANI. Paris: Masson et Cie. 1932. Pp. 187. Price 20 fr.

The former popularity of electricity in the treatment of various nervous disorders has been succeeded, in England at least, by considerable scepticism as to its value, but newer discoveries, more efficient apparatus and other methods of its application present the possibility that in certain cases it may be of therapeutic use. These are discussed shortly in this volume, and though the authors express enthusiasm for some of the results that can be obtained, their attitude is not wholly uncritical.

In addition to the forms of treatment with which all physicians are acquainted, they discuss the value of X-rays in cerebral and pituitary tumours, syringomyelia, the acute stages of poliomyelitis and in other conditions, as well as transcerebral ionization and diathermy, the latter reputed to be useful in some cases of encephalitis lethargica and paralysis agitans. The technique of the various methods of treatment and dosage are adequately described. The use and value of hydrotherapy, massage and other forms of physical treatment are also dealt with.

As the subject matter is arranged mainly under diseases, the book will be a handy guide for those who consult it for practical ends.

Neurofibromatose. Von R. KIENBÖCH und H. RÖSLER. S. 52. Leipzig: G. Thieme. 1932. Price 9.80 m.

With praiseworthy conciseness the authors review the features of neurofibromatosis as revealed in literature and illustrated by their own cases. The points on which most emphasis is laid are the frequency of large intrathoracic tumours of the same structure and origin as neurofibromata in other organs, and changes in bones in Recklinghausen's disease.

Other clinical aspects of the condition and its pathology are adequately discussed too. It is rarely one's fortune nowadays to meet a monograph, in the German language at least, so concisely and lucidly written and so excellently produced.

Les Abcès cérébraux et leur Traitement. Par JEAN PIQUET. Paris: Masson et Cie. 1931. Price 22 fr.

This little volume in the series of "Médecine et Chirurgie Pratique" gives a clear and concise account of the ætiology, pathogenesis, symptomatology and treatment of intracranial abscess. The clinical descriptions given, however, are those of the terminal stages of the condition and will not assist materially to that early diagnosis which is so essential to favourable results from treatment. There is a full table of contents, but no index.

Die juvenile amaurotische Idiotie. Von TORSTEN SJÖGREN. Lund: Berlingska Boktryckeriet. 1931. S. 425. Price kr. 10.

In this monograph the author has collected the extraordinary number of 120 cases of juvenile amaurotic idiocy occurring in 62 Swedish families, 10 of which were inter-related. By tracing many of the families back through six or seven generations, he has been able to study the Mendelian characters of the disease by Weinberg's method and has found it to be transmitted as a mono-hybrid recessive. He found no evidence of hereditary relationship between the juvenile and the infantile forms of the disease, but there was an unusually heavy incidence of epilepsy, imbecility and schizophrenia in earlier generations of affected families. As might be expected from the Mendelian character of the disease, consanguinity of parents was common; in over 25 per cent. of cases the parents had common grandparents or great grandparents. There was also a tendency for the cases to be grouped in certain localities.

Post-mortem material of 9 cases was available, and is to form the basis of a study by Professor Sjovall. Brain puncture was made in a further 9 cases to establish the diagnosis. The author has availed himself to the full of the advantages for the study of the disease which his country offers, and his monograph is a great addition to our knowledge of what appears to be in most countries a rare disease.

Handbuch der Geisteskrankheiten. Herausgegeben von OSWALD BUMKE. Band 8. Spez. Teil IV. Mit 70 Abbildungen. S. 751. Berlin: Springer. 1930. Price 76 Rm.

In this large and very detailed volume of Bumke's "System of Psychiatry" the syphilitic, arteriosclerotic, senile and epileptic disorders are described with thoroughness.

Professor Hauptmann deals with the ætiology and pathogenesis in syphilitic psychoses, showing how much is still obscure in this field. Wilmann's views as to the relation between intensive early anti-syphilitic treatment and the incidence of G.P.I. are discussed fully. The lengthy monographs on luetic psychoses and general paralysis which follow are by Bostroem. After pointing out the relative infrequency of mental disorder due to cerebral syphilis, he deals with the tabetic psychoses (which he repudiates), syphilitic epilepsy and

dementia as either a residual or a chronic progressive manifestation of the disease; he gives a valuable account of luetic psychoses which appear as schizophrenic, affective and other endogenous reactions. A full description of the clinical features and the diagnosis of G.P.I. occupies more than a fifth of the whole volume; with the succeeding chapter by Plaut and Kihn on the treatment of these conditions it constitutes the most complete available exposition of G.P.I. and the other syphilitic psychoses. The treatment by infection with malaria is reviewed, and such other methods as inoculation with relapsing fever and sodoku, use of specific drugs, proteins and vaccines are appraised.

Stern's section on arteriosclerotic psychoses shows how intimately neurological and psychiatric data are intermingled in these disorders, as also in the involutional psychoses, which are described by W. Runge. The depressive and paranoid states of the climacteric are a classic battlefield in psychiatric nosology and pathology, but the presentation here is in conformity with modern usage which sees in these conditions a varying complex of other types of reaction. In the chapter on senile psychoses Pick's disease and Alzheimer's disease are also described. The volume concludes with a summary by Gruhle of the present position with regard to epilepsy, in which the problem of epileptoid psychopathy receives special attention. It is doubtful if the author can be followed in his assertion that an operation is always indicated where the attack is chiefly characterized, or regularly ushered in, by definite focal symptoms. In this section, as indeed throughout the volume, the familiarity of each writer with an enormous literature is continually in evidence; the soundness and completeness of the work testify to this and to the authority of the writers in their respective fields.

Methoden der Psychologie des Gefühlslebens. Von GUSTAV STÖRRING. Abderhalden's Handbuch der biologischen Arbeitsmethoden. Abt. VI. Teil B., 2 Hälfte. Hefte 2, 3, 4. S. 1125-1646. Berlin: Urban and Schwarzenberg. 1931. Price Rm. 26.70.

The methods of experimental psychology are being described in the Abderhalden series with the same thoroughness as those dealing with more readily measurable and conclusive data. The present contribution is by Störring. The first part deals with the general theory of feeling. The author points out that introspection, experiment and observation of the abnormal are the chief methods available. It soon becomes clear, however, that the study of morbid psychological phenomena by the analytical method bulks largest in its presentation, so that the greater part of the work might well serve as an account of the psychopathology of affect. Two sections are devoted to various experimental procedures and to data obtained by introspection, but there is no reference to the valuable English work in this field, and the author's quarrel with "Gestalt" psychology narrows the range of the experimental methods recorded. In the second part the methods of investigating the psychology of

judgment in regard to æsthetic and ethical value are discussed; for the latter the ethnological approach is considered valuable, as used by Wundt and Westermarck, while deductive as well as the familiar inductive individual methods are described.

Ergebnisse der Reiztherapie bei progressiver Paralyse. Herausgegeben von K. BONHOEFFER und P. JOSSMAN. Pp. 154. Berlin: S. Karger. 1932. Price M. 14.80.

Wagner-Jauregg's discovery is still recent enough to make competent reports on it a matter of practical importance. The value of the malaria method is now assured, but in its elaboration, combination with other infections or with drugs, its social implications and clinical effects there are still many unsettled points. In this volume over two thousand cases of general paralysis, treated in Berlin between 1922 and 1929, form the material for a wide survey of the results obtained by various methods. A number of writers from different clinics and mental hospitals contribute to the work, their general conclusions being summed up by Jossman. In 40 per cent. of the cases there was improvement, in 23 per cent. practical recovery. In a large number the abnormal serological findings cleared up after pyrexial therapy, without use of anti-syphilitic remedies. The chief adjuncts or substitutes for the familiar malarial treatment were sulfosin, repeated inoculation with malaria and spirochætal vaccines. The paranoid-hallucinatory forms which may follow treatment are discussed, and there are final chapters on the pathology and social aspects of the disease.

L'Evolution psychiatrique. Par plusieurs auteurs. 1931. Paris: Maloine. Pp. 105. Price 16 fr.

The present work is the production of that small circle of French psychopathologists whose troubled history has recently been told by E. Minkowski.

The first paper, by H. Codet, is on "Les Emotifs et les Impressionables." It is refreshing to find a French author who recognizes the artificial nature of any division of anxiety reactions into vagotonic and sympathicotonic; in the vagotonic variety here described depressive features appear to predominate. P. Guiraud's rather rambling report of some cases of murder without apparent motive is followed by an appreciative account by E. Minkowski of the psychiatric work of Maurice Mignard, whose early death was so deplored by the few familiar with his researches into schizophrenia and psychopathology in general. M. Montassut writes on neurasthenic fatigue, regarded as a form of chronic alkalosis, and Sophie Morgenstern gives the conventional psycho-analytic views on the important "depersonalization" syndrome.

Psychopathic Personalities. By EUGEN KAHN. Pp. 521. New Haven: Yale University Press. Humphrey Milford. 1931. Price 22s. 6d.

This book has already been noticed here, when it appeared as a contribution to Bumke's "Handbuch der Psychiatrie." It represents an effort to cope with the difficulties of classifying personality, and especially its morbid variants. The clinical part is sober and detailed. The translation is too often reminiscent of the original German. There is no alphabetical index of subjects.

The Psychology of Men of Genius. By ERNST KRETSCHMER. London: Kegan Paul. 1931. Pp. 256. Price 15s.

This book of Kretschmer's, like most of his writings, is vivid and original rather than convincing. It is well written, but more likely to stimulate the casual reader than to satisfy the specialist. The relation of special endowment to mental disorder is an old question, and from the now urgent standpoint of eugenics a very important one, but it can better be studied by statistical and genealogical methods than by belletristic guesses or unproven assumptions about racial and constitutional attributes. So long as the work is recognized as a brilliant essay and not regarded as typifying the methods of modern psychological study, it may be read with profit.

The Problem of Genius. By W. LANGE-EICHBAUM. Translated by Eden and Cedar Paul. Pp. 187. London: Kegan Paul. 1931. Price 8s. 6d.

This is a well-translated summary of the conclusions reached by Lange-Eichbaum in his larger work "Genie, Irrsin und Ruhm." He points out how mutable a value genius represents, and how necessary it is to recognize its accidental and transitory aspects. Fame, talent, insanity and civilization are the topics in relation to which genius is discussed with a lucidity by no means superficial. Many authorities would question the author's general statement that "nine-tenths of genius is intimately associated with psychopathy or psychosis," but there is much to support his views as to the influence of mental disorder, where present, upon the manifestations of genius.

Körperlich-seelische Zusammenhänge in Gesundheit und Krankheit. Von WALTER H. v. WYSS. Pp. 128. Leipzig: Georg Thieme. 1931.

Dualistic studies of the relation between mind and body are as yet far from satisfying the physiologist or the philosopher. Dr. von Wyss directs his little book to doctors, who are seldom either. The influence of the newer

schools is evident in the theoretical part, but he has avoided the stumbling-block of metaphysics, and wisely contented himself with assembling our available knowledge on the bodily concomitants of mental states, especially as to mood and expression. It is impossible to read this thoughtful and informative contribution to medical psychology without being impressed by the necessity for regarding function and the total integrated person as more important than isolated structures.

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EDITOR.